

INVESTOR IN PEOPLE

The Patent Office
 Concept House
 Cardiff Road
 Newport
 South Wales
 NP10 8QQ

**PRIORITY
 DOCUMENT**
 SUBMITTED OR TRANSMITTED IN
 COMPLIANCE WITH RULE 17.1(a) OR (b)

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

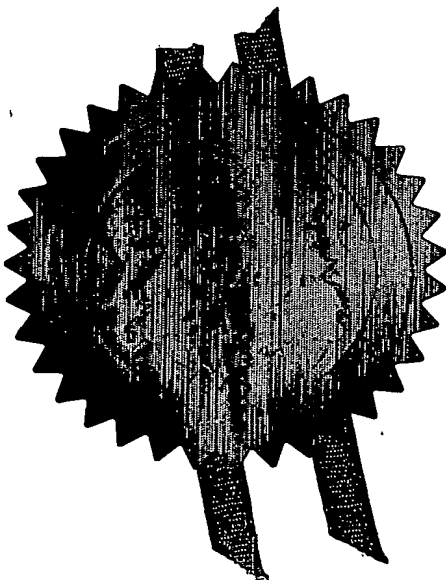
In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

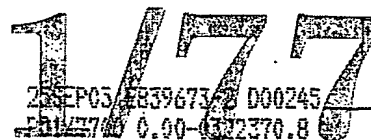
In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed *ANB*

Dated 13 February 2004





Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales NP10 8QQ

1.	Your reference	4-32910P3		
2.	Patent application number (The Patent Office will fill in this part)	0322370.8		24 SEP 2003
3.	Full name, address and postcode of the or of each applicant (underline all surnames)	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND		
	Patent ADP number (if you know it)			
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND		
4.	Title of invention	Organic compounds		
5.	Name of your agent (If you have one)	Craig McLean		
	"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham, West Sussex RH12 5AB		
	Patents ADP number (if you know it)	07181522002		
6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application		Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if: a) any applicant named in part 3 is not an inventor, or b) there is an inventor who is not named as an applicant, or c) any named applicant is a corporate body. (see note (d))	Yes		

7125487005

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form

Description 61.

Claim(s) 8

Abstract

Drawing(s)

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

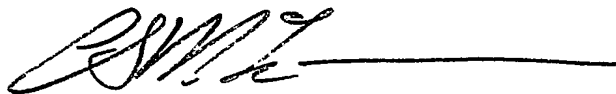
Any other documents
(please specify)

11.

I/We request the grant of a patent on the basis of this application

Signature

Date



Craig McLean

24th September 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Mr. Trevor Drew

01403 323069

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

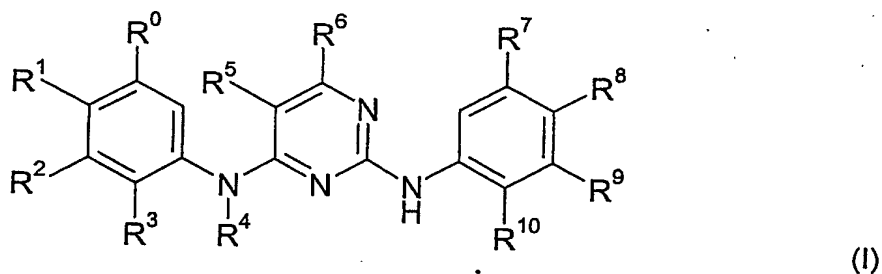
Notes

- If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.
- Write your answers in capital letters using black ink or you may type them.
- ~~If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.~~
- Once you have filled in the form you must remember to sign and date it.
- For details of the fee and ways to pay please contact the Patent Office.

Organic Compounds

The present invention relates to novel pyrimidine derivatives, to processes for their production, their use as pharmaceuticals and to pharmaceutical compositions comprising them.

More particularly the present invention provides in a first aspect, a compound of formula I



wherein

each of R^0 , R^1 , R^2 , and R^3 independently is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkinyl, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkyl C_1 - C_8 alkyl, C_5 - C_{10} aryl C_1 - C_8 alkyl, hydroxy C_1 - C_8 alkyl, C_1 - C_8 alkoxy C_1 - C_8 alkyl, amino C_1 - C_8 alkyl, halo C_1 - C_8 alkyl, unsubstituted or substituted C_5 - C_{10} aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1, 2 or 3 hetero atoms selected from N, O and S, hydroxy, C_1 - C_8 alkoxy, hydroxy C_1 - C_8 alkoxy, C_1 - C_8 alkoxy C_1 - C_8 alkoxy, halo C_1 - C_8 alkoxy, unsubstituted or substituted C_5 - C_{10} aryl C_1 - C_8 alkoxy, unsubstituted or substituted heterocyclloxy, or unsubstituted or substituted heterocyclyl C_1 - C_8 alkoxy, unsubstituted or substituted amino, C_1 - C_8 alkylthio, C_1 - C_8 alkylsulfinyl, C_1 - C_8 alkylsulfonyl, C_5 - C_{10} arylsulfonyl, halogen, carboxy, C_1 - C_8 alkoxycarbonyl, unsubstituted or substituted carbamoyl, unsubstituted or substituted sulfamoyl, cyano or nitro;

or R^0 and R^1 , R^1 and R^2 , and/or R^2 and R^3 form, together with the carbon atoms to which they are attached, a 5 or 6 membered carbocyclic or heterocyclic ring comprising 0, 1, 2 or 3 heteroatoms selected from N, O and S;

R^4 is hydrogen or C_1 - C_8 alkyl;

each of R^5 and R^6 independently is hydrogen, C_1 - C_8 alkyl, C_1 - C_8 alkoxy C_1 - C_8 alkyl, halo C_1 - C_8 alkyl, C_1 - C_8 alkoxy, halogen, carboxy, C_1 - C_8 alkoxycarbonyl, unsubstituted or substituted carbamoyl, cyano, or nitro;

each of R^7 , R^8 , R^9 , and R^{10} independently is C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkinyl, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkyl C_1 - C_8 alkyl, C_5 - C_{10} aryl C_1 - C_8 alkyl, hydroxy C_1 - C_8 alkyl, C_1 - C_8 alkoxy C_1 - C_8 alkyl, amino C_1 - C_8 alkyl, halo C_1 - C_8 alkyl, unsubstituted or substituted C_5 - C_{10} aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1, 2 or 3

hetero atoms selected from N, O and S, hydroxy, C₁-C₈alkoxy, hydroxyC₁-C₈alkoxy, C₁-C₈alkoxyC₁-C₈alkoxy, haloC₁-C₈alkoxy, unsubstituted or substituted C₅-C₁₀arylC₁-C₈alkoxy, unsubstituted or substituted heterocycloxy, or unsubstituted or substituted heterocyclylC₁-C₈alkoxy, unsubstituted or substituted amino, C₁-C₈alkylthio, C₁-C₈alkylsulfinyl, C₁-C₈alkylsulfonyl, C₅-C₁₀arylsulfonyl, halogen, carboxy, C₁-C₈alkoxycarbonyl, unsubstituted or substituted carbamoyl, unsubstituted or substituted sulfamoyl, cyano or nitro; wherein R⁷, R⁸ and R⁹ independently of each other can also be hydrogen; or R⁷ and R⁸, R⁸ and R⁹, and/or R⁹ and R¹⁰ form together with the carbon atoms to which they are attached, a 5 or 6 membered carbocyclic or heterocyclic ring comprising 0, 1, 2 or 3 heteroatoms selected from N, O and S; and salts thereof.

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated:

Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt, or the like.

Any asymmetric carbon atoms may be present in the (R)-, (S)- or (R,S)-configuration, preferably in the (R)- or (S)-configuration. The compounds may thus be present as mixtures of isomers or as pure isomers, preferably as enantiomer-pure diastereomers.

The invention relates also to possible tautomers of the compounds of formula I.

C₁-C₈alkyl denotes a an alkyl radical having from 1 up to 8, especially up to 4 carbon atoms, the radicals in question being either linear or branched with single or multiple branching; preferably, C₁-C₈alkyl is butyl, such as n-butyl, sec-butyl, isobutyl, tert-butyl, propyl, such as n-propyl or isopropyl, ethyl or methyl; especially methyl, propyl or tert-butyl.

C₂-C₈alkenyl denotes a an alkenyl radical having from 2 up to 8, especially up to 5 carbon atoms, the radicals in question being either linear or branched with single or multiple branching; preferably, C₂-C₈alkenyl is pentenyl, such as 3-methyl-2-buten-2-yl, butenyl, such as 1- or 2-butenyl or 2-buten-2-yl, propenyl, such as 1-propenyl or allyl, or vinyl.

C₂-C₈alkynyl denotes a an alkynyl radical having from 2 up to 8, especially up to 5 carbon atoms, the radicals in question being either linear or branched; preferably, C₂-C₈alkynyl is propinyl, such as 1-propinyl or propargyl, or acetylenyl.

C₃-C₈cycloalkyl denotes a cycloalkyl radical having from 3 up to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl, preferably cyclopropyl, cyclopentyl or cyclohexyl.

C₁-C₈alkoxy is especially methoxy, ethoxy, isopropoxy, or tert-butoxy.

HydroxyC₁-C₈alkyl is especially hydroxymethyl, 2-hydroxyethyl or 2-hydroxy-2-propyl.

HydroxyC₁-C₈alkoxy is especially 2-hydroxyethoxy or 3-hydroxypropoxy.

C₁-C₈alkoxyC₁-C₈alkoxy is especially 2-methoxyethoxy.

C₁-C₈alkoxyC₁-C₈alkyl is especially methoxymethyl, 2-methoxyethyl or 2-ethoxyethyl.

Halogen is preferably fluorine, chlorine, bromine, or iodine, especially fluorine, chlorine, or bromine.

HaloC₁-C₈alkyl is preferably chloroC₁-C₈alkyl or fluoroC₁-C₈alkyl, especially trifluoromethyl or pentafluoroethyl.

HaloC₁-C₈alkoxy is preferably chloroC₁-C₈alkoxy or fluoroC₁-C₈alkoxy, especially trifluoromethoxy.

C₁-C₈alkoxycarbonyl is especially tert-butoxycarbonyl, iso-propoxycarbonyl, methoxycarbonyl or ethoxycarbonyl.

Unsubstitued or substituted carbamoyl is carbamoyl substituted by one or two substituents selected from hydrogen, C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₃-C₈cycloalkyl, C₃-C₈cycloalkylC₁-C₈alkyl, C₅-C₁₀arylC₁-C₈alkyl, hydroxyC₁-C₈alkyl, C₁-C₈alkoxyC₁-C₈alkyl, haloC₁-C₈alkyl, unsubstitued or substituted C₅-C₁₀aryl, or aminoC₁-C₈alkyl, or carbamoyl wherein the

substituents and the nitrogen atom of the carbamoyl group represent a 5 or 6 membered heterocyclyl further comprising 0, 1 or 2 hetero atoms selected from N, O and S; and is preferably carbamoyl, methylcarbamoyl, dimethylcarbamoyl, propylcarbamoyl, hydroxyethyl-methyl-carbamoyl, di(hydroxyethyl)carbamoyl, dimethylaminoethylcarbamoyl, or pyrrolidinocarbonyl, piperidinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, especially carbamoyl or dimethylcarbamoyl.

Unsubstituted or substituted sulfamoyl is sulfamoyl substituted by one or two substituents selected from hydrogen, C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkinyl, C₃-C₈cycloalkyl, C₃-C₈cycloalkylC₁-C₈alkyl, C₅-C₁₀arylC₁-C₈alkyl, hydroxyC₁-C₈alkyl, C₁-C₈alkoxyC₁-C₈alkyl, haloC₁-C₈alkyl, unsubstituted or substituted C₅-C₁₀aryl, or aminoC₁-C₈alkyl, or sulfamoyl wherein the substituents and the nitrogen atom of the sulfamoyl group represent a 5 or 6 membered heterocyclyl further comprising 0, 1 or 2 hetero atoms selected from N, O and S; and is preferably sulfamoyl, methylsulfamoyl, propylsulfamoyl, cyclopropylmethyl-sulfamoyl, 2,2,2-trifluoroethylsulfamoyl, dimethylaminoethylsulfamoyl, dimethylsulfamoyl, hydroxyethyl-methyl-sulfamoyl, di(hydroxyethyl)sulfamoyl, or pyrrolidinosulfonyl, piperidinosulfonyl, N-methylpiperazinosulfonyl or morpholinosulfonyl, especially sulfamoyl or methylsulfamoyl.

Unsubstituted or substituted amino is amino substituted by one or two substituents selected from hydrogen, C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkinyl, C₃-C₈cycloalkyl, C₃-C₈cycloalkylC₁-C₈alkyl, C₅-C₁₀arylC₁-C₈alkyl, hydroxyC₁-C₈alkyl, C₁-C₈alkoxyC₁-C₈alkyl, haloC₁-C₈alkyl, unsubstituted or substituted C₅-C₁₀aryl, aminoC₁-C₈alkyl, acyl, e.g. formyl, C₁-C₈alkylcarbonyl, C₅-C₁₀arylcarbonyl, C₁-C₈alkylsulfonyl or C₅-C₁₀arylsulfonyl, and is preferably amino, methylamino, dimethylamino, propylamino, benzylamino, hydroxyethyl-methyl-amino, di(hydroxyethyl)amino, dimethylaminoethylamino, acetylamino, acetyl-methyl-amino, benzoylamino, methylsulfonylamino or phenylsulfonylamino, especially amino or dimethylamino.

AminoC₁-C₈alkyl is especially aminoethyl, methylaminoethyl, dimethylaminoethyl or dimethylaminopropyl.

Unsubstituted or substituted C₅-C₁₀aryl is, for example, phenyl, indenyl, indanyl, naphthyl, or 1,2,3,4-tetrahydronaphthalenyl, optionally substituted by C₁-C₈alkyl, C₁-C₈alkoxyC₁-C₈alkyl, haloC₁-C₈alkyl, hydroxy, C₁-C₈alkoxy, methylenedioxy, amino, substituted amino, halogen, carboxy, C₁-C₈alkoxycarbonyl, carbamoyl, sulfamoyl, cyano or nitro; preferably phenyl, tolyl,

trifluoromethylphenyl, methoxyphenyl, dimethoxyphenyl, methylenedioxyphenyl, chlorophenyl or bromophenyl, whereby the substituents may be in ortho, meta or para position, preferably meta or para.

C₅-C₁₀aryloxy is especially phenoxy or methoxyphenoxy, e.g. p-methoxyphenoxy.

C₅-C₁₀arylC₁-C₈alkyl is especially benzyl or 2-phenylethyl.

C₅-C₁₀arylC₁-C₈alkoxy is especially benzyloxy or 2-phenylethoxy.

Unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1, 2 or 3 hetero atoms selected from N, O and S may be unsaturated, partially unsaturated or saturated, and further condensed to a benzo group or a 5 or 6 membered heterocyclyl group, and may be bound through a hetero or a carbon atom, and is, for example, pyrrolyl, indolyl, pyrrolidinyl, imidazolyl, benzimidazolyl, pyrazolyl, triazolyl, benzotriazolyl, tetrazolyl, pyridyl, quinoliny, isoquinoliny, 1,2,3,4-tetrahydroquinoliny, piperidyl, pyrimidinyl, pyrazinyl, piperazinyl, purinyl, tetrazinyl, oxazolyl, isoxalyl, morpholiny, thiazolyl, benzothiazolyl, oxadiazolyl, and benzoxadiazolyl. Substituents considered are C₁-C₈alkyl, hydroxyC₁-C₈alkyl, C₁-C₈alkoxyC₁-C₈alkyl, C₁-C₈alkoxyC₁-C₈alkoxy, haloC₁-C₈alkyl, hydroxy, amino, substituted amino, C₁-C₈alkoxy, halogen, carboxy, C₁-C₈alkylcarbonyl, C₁-C₈alkoxycarbonyl, carbamoyl, C₁-C₈alkylcarbamoyl, cyano, oxo, or unsubstituted or substituted 5 or 6 membered heterocyclyl as defined in this paragraph. 5 or 6 membered heterocyclyl preferably comprises 1 or 2 hetero atoms selected from N, O and S, and is especially indolyl, pyrrolidinyl, pyrrolidonyl, imidazolyl, N-methylimidazolyl, benzimidazolyl, S,S-dioxoisothiazolidinyl, piperidyl, 4-acetylamino piperidyl, 4-methylcarbamoylpiperidyl, 4-piperidinopiperidyl, 4-cyanopiperidyl, piperazinyl, N-methylpiperazinyl, N-(2-hydroxyethyl)piperazinyl, morpholiny, 1-aza-2,2-dioxo-2-thiacyclohexyl, or sulfolanyl.

In unsubstituted or substituted heterocycliloxy, heterocyclyl has the meaning as defined above, and is especially N-methyl-4-piperidiloxy. In unsubstituted or substituted heterocyclylC₁-C₈alkoxy, heterocyclyl has the meaning as defined above, and is especially 2-pyrrolidinoethoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 1-methyl-piperidin-3-ylmethoxy, 3-(N-methylpiperazino)propoxy or 2-(1-imidazolyl)ethoxy.

In a 5 or 6 membered carbocyclic or heterocyclic ring comprising 0, 1, 2 or 3 heteroatoms selected from N, O and S, and formed by two adjacent substituents together with the benzene ring, the ring may be further substituted, e.g. by C₁-C₈alkyl, C₁-C₈alkoxy, haloC₁-C₈alkyl, hydroxy, amino, substituted amino, C₁-C₈alkoxy, halogen, carboxy, C₁-C₈alkoxycarbonyl, carbamoyl, cyano, or oxo. The two adjacent substituents forming such a ring are preferably propylene, butylene, 1-aza-2-propylidene, 3-aza-1-propylidene, 1,2-diaza-2-propylidene, 2,3-diaza-1-propylidene, 1-oxapropylene, 1-oxapropylidene, methylenedioxy, difluoromethylenedioxy, 2-aza-1-oxopropylene, 2-aza-2-methyl-1-oxopropylene, 1-aza-2-oxopropylene, 2-aza-1,1-dioxo-1-thiapropylene or the corresponding butylene derivatives forming a 6 membered ring.

Salts are especially the pharmaceutically acceptable salts of compounds of formula I.

Such salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula I with a basic nitrogen atom, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, 2-, 3- or 4-methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable in the form of pharmaceutical preparations), and these are therefore preferred.

In view of the close relationship between the novel compounds in free form and those in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, any reference to the free compounds hereinbefore and hereinafter is to be understood as referring also to the corresponding salts, as appropriate and expedient.

The compounds of formula I have valuable pharmacological properties, as described hereinbefore and hereinafter.

In formula I the following significances are preferred independently, collectively or in any combination or sub-combination:

- (a) each of R^0 or R^2 independently is hydrogen, C_1 - C_8 alkyl, e.g. methyl, ethyl or isopropyl, hydroxy C_1 - C_8 alkyl, e.g. hydroxyethyl or hydroxybutyl, halo C_1 - C_8 alkyl, e.g. trifluoromethyl, unsubstituted or substituted C_5 - C_{10} aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1 - C_8 alkoxy, e.g. methoxy, ethoxy or isopropoxy, halo C_1 - C_8 alkoxy, e.g. trifluoromethoxy, C_5 - C_{10} aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclyl C_1 - C_8 alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, C_1 - C_8 alkylsulfonyl, e.g. methylsulfonyl, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably hydrogen, piperazino, N-methylpiperazino or 1-methyl-4-piperidyloxy, in particular hydrogen;
- (b) R^1 is hydrogen, C_1 - C_8 alkyl, e.g. methyl, ethyl or isopropyl, hydroxy C_1 - C_8 alkyl, e.g. hydroxyethyl or hydroxybutyl, halo C_1 - C_8 alkyl, e.g. trifluoromethyl, unsubstituted or substituted C_5 - C_{10} aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1 - C_8 alkoxy, e.g. methoxy, ethoxy or isopropoxy, halo C_1 - C_8 alkoxy, e.g. trifluoromethoxy, C_5 - C_{10} aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclyl C_1 - C_8 alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-

- morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, C₁-C₈alkylsulfonyl, e.g. methylsulfonyl, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably hydrogen, piperazino, N-methylpiperazino, morpholino, 1-methyl-4-piperidinyloxy, 3-morpholinopropoxy or 2-morpholinoethoxy, in particular hydrogen;
- (c) R³ is hydrogen, C₁-C₈alkyl, e.g. methyl or ethyl, hydroxyC₁-C₈alkyl, e.g. hydroxyethyl or hydroxybutyl, haloC₁-C₈alkyl, e.g. trifluoromethyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 heteroatoms selected from N, O and S, e.g. 2-pyrrolidonyl or S,S-dioxoisothiazolidinyl, C₁-C₈alkoxy, e.g. methoxy, substituted amino, e.g. acetylamino, acetyl-methyl-amino, benzoylamino, methylsulfonylamino or phenylsulfonylamino, C₁-C₈alkylsulfonyl, e.g. methylsulfonyl, C₅-C₁₀arylsulfonyl, e.g. phenylsulfonyl, halogen, e.g. fluoro or chloro, carboxy, substituted or unsubstituted carbamoyl, e.g. carbamoyl, methylcarbamoyl or dimethylcarbamoyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl, propylsulfamoyl, isopropylsulfamoyl, isobutylsulfamoyl, cyclopropylmethyl-sulfamoyl, 2,2,2-trifluoroethylsulfamoyl, dimethylsulfamoyl or morpholinosulfonyl; preferably sulfamoyl, methylsulfamoyl or propylsulfamoyl;
- (d) each pair of adjacent substituents R⁰ and R¹, or R¹ and R², or R² and R³ are -CH₂-NH-CO-, -CH₂-CH₂-NH-CO-, -CH₂-CO-NH-, -CH₂-CH₂-CO-NH-, -CH₂-NH-SO₂-, -CH₂-CH₂-NH-SO₂-, -CH₂-SO₂-NH-, -CH₂-CH₂-SO₂-NH-, -CH₂-CH₂-SO₂-, -CH₂-CH₂-CH₂-SO₂-, -O-CH₂-O-, or -O-CF₂-O-, and such pairs wherein hydrogen in NH is replaced by C₁-C₈alkyl; preferably the pair of adjacent substituents R⁰ and R¹, or R¹ and R² being -O-CH₂-O-, and the pair of adjacent substituents R² and R³ being -CH₂-NH-CO- or -CH₂-NH-SO₂-.
- (e) R⁴ is hydrogen or C₁-C₈alkyl, e.g. methyl; preferably hydrogen;
- (f) R⁵ is hydrogen; C₁-C₈alkyl, e.g. methyl or ethyl, halogen, e.g. chloro or bromo, haloC₁-C₈alkyl, e.g. trifluoromethyl, cyano or nitro; preferably hydrogen, methyl, ethyl, chloro, bromo, trifluoromethyl or nitro; in particular chloro or bromo;
- (g) R⁶ is hydrogen;
- (h) each of R⁷ and R⁸ independently is hydrogen, C₁-C₈alkyl, e.g. methyl, ethyl or isopropyl, hydroxyC₁-C₈alkyl, e.g. hydroxyethyl or hydroxybutyl, haloC₁-C₈alkyl, e.g. trifluoromethyl, unsubstituted or substituted C₅-C₁₀aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C₁-C₈alkoxy, e.g.

methoxy, ethoxy or isopropoxy, haloC₁-C₈alkoxy, e.g. trifluoromethoxy, C₅-C₁₀aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC₁-C₈alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, C₁-C₈alkylsulfonyl, e.g. methylsulfonyl, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably hydrogen, methyl, isopropyl, trifluoromethyl, phenyl, methoxyphenyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, isopropoxy, phenoxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 2-(1-imidazolyl)ethoxy, dimethylamino, fluoro, morpholinocarbonyl, piperidinocarbonyl, piperazinocarbonyl or cyclohexylcarbamoyl;

- (i) R⁸ is hydrogen, C₁-C₈alkyl, e.g. methyl, ethyl or isopropyl, hydroxyC₁-C₈alkyl, e.g. hydroxyethyl or hydroxybutyl, haloC₁-C₈alkyl, e.g. trifluoromethyl, C₅-C₁₀aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C₁-C₈alkoxy, e.g. methoxy, ethoxy or isopropoxy, haloC₁-C₈alkoxy, e.g. trifluoromethoxy, C₅-C₁₀aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC₁-C₈alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino or dimethylamino, C₁-C₈alkylsulfonyl, e.g. methylsulfonyl, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl, cyano, or nitro; preferably hydrogen, methyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, trifluoromethoxy, phenoxy, 1-methyl-4-piperidyloxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 3-(N-methylpiperazino)-propoxy, methylamino, fluoro, chloro, sulfamoyl or nitro;
- (j) R¹⁰ is C₁-C₈alkyl, e.g. methyl, ethyl or butyl, hydroxyC₁-C₈alkyl, e.g. hydroxyethyl or hydroxybutyl, haloC₁-C₈alkyl, e.g. trifluoromethyl, C₁-C₈alkoxy, e.g. methoxy or ethoxy, unsubstituted or substituted heterocyclylC₁-C₈alkoxy, e.g. 2-(1-imidazolyl)ethoxy, unsubstituted or substituted amino, e.g. methylamino or dimethylamino, halogen, e.g. fluoro or chloro; carboxy, carbamoyl, or unsubstituted or substituted sulfamoyl, e.g. sulfamoyl,

- methylsulfamoyl or dimethylsulfamoyl; preferably methyl, butyl, methoxy, ethoxy, 2-(1-imidazolyl)ethoxy, methylamino, dimethylamino or fluoro; and
- (k) each pair of adjacent substituents R^7 and R^8 , or R^8 and R^9 or R^9 and R^{10} , are $-NH-CH=CH-$, $-CH=CH-NH-$, $-NH-N=CH-$, $-CH=N-NH-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-O-$, $-CH=CH-O-$, $-O-CH_2-O-$, or $-O-CF_2-O-$; preferably the pair of adjacent substituents R^7 and R^8 or R^8 and R^9 being $-O-CH_2-O-$ or the pair of adjacent substituents R^9 and R^{10} being $-NH-CH=CH-$, $-CH=N-NH-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$ or $-O-CF_2-O-$.

More preferred are the following meanings, independently, collectively or in any combination or sub-combination:

- (a') each of R^0 or R^2 independently is hydrogen, C_1-C_8 alkyl, e.g. methyl, ethyl or isopropyl, halo C_1-C_8 alkyl, e.g. trifluoromethyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1-C_8 alkoxy, e.g. methoxy, ethoxy or isopropoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclyl C_1-C_8 alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, halogen, e.g. fluoro or chloro; preferably hydrogen, piperazino, N-methylpiperazino or 1-methyl-4-piperidyloxy, in particular hydrogen;
- (b') R^1 is hydrogen, C_1-C_8 alkyl, e.g. methyl, ethyl or isopropyl, halo C_1-C_8 alkyl, e.g. trifluoromethyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1-C_8 alkoxy, e.g. methoxy, ethoxy or isopropoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclyl C_1-C_8 alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, halogen, e.g. fluoro or chloro; preferably hydrogen, piperazino, N-methylpiperazino, morpholino, 1-methyl-4-piperidyloxy, 3-morpholinopropoxy or 2-morpholinoethoxy, in particular hydrogen;
- (c') R^3 is hydrogen, C_1-C_8 alkyl, e.g. methyl or ethyl, halo C_1-C_8 alkyl, e.g. trifluoromethyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 heteroatoms selected from N, O and S, e.g. 2-pyrrolidonyl or S,S-dioxoisothiazolidinyl, C_1-C_8 alkoxy, e.g. methoxy, substituted amino, e.g. acetylamino, acetyl-methyl-amino, benzoylamino,

methylsulfonylamino or phenylsulfonylamino, C₁-C₈alkylsulfonyl, e.g. methylsulfonyl, C₅-C₁₀arylsulfonyl, e.g. phenylsulfonyl, halogen, e.g. fluoro or chloro, carboxy, substituted or unsubstituted carbamoyl, e.g. carbamoyl, methylcarbamoyl or dimethylcarbamoyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl, propylsulfamoyl, isopropylsulfamoyl, isobutylsulfamoyl, cyclopropylmethyl-sulfamoyl, 2,2,2-trifluoroethylsulfamoyl, dimethylsulfamoyl or morpholinosulfonyl; preferably sulfamoyl, methylsulfamoyl or propylsulfamoyl;

(d') each pair of adjacent substituents R⁰ and R¹, or R¹ and R², or R² and R³ are -CH₂-NH-CO-, -CH₂-NH-SO₂-, -CH₂-CH₂-SO₂-, -O-CH₂-O-, or -O-CF₂-O-, and such pairs wherein hydrogen in NH is replaced by C₁-C₈alkyl; preferably the pair of adjacent substituents R⁰ and R¹, or R¹ and R² being -O-CH₂-O-, and the pair of adjacent substituents R² and R³ being -CH₂-NH-CO- or -CH₂-NH-SO₂-.

(e') R⁴ is hydrogen;

(f') R⁵ is hydrogen, halogen, e.g. chloro or bromo, haloC₁-C₈alkyl, e.g. trifluoromethyl, or nitro; preferably hydrogen, chloro, bromo, trifluoromethyl or nitro; in particular chloro or bromo;

(g') R⁶ is hydrogen;

(h') each of R⁷ and R⁹ independently is hydrogen, C₁-C₈alkyl, e.g. methyl, ethyl or isopropyl, haloC₁-C₈alkyl, e.g. trifluoromethyl, unsubstituted or substituted C₅-C₁₀aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C₁-C₈alkoxy, e.g. methoxy, ethoxy or isopropoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC₁-C₈alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably hydrogen, methyl, isopropyl, trifluoromethyl, phenyl, o-, m- or p-methoxyphenyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, isopropoxy, phenoxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 2-(1-imidazolyl)ethoxy, dimethylamino, fluoro, morpholinocarbonyl, piperidinocarbonyl, piperazinocarbonyl or cyclohexylcarbamoyl;

(i') R⁸ is hydrogen, C₁-C₈alkyl, e.g. methyl, ethyl or isopropyl, haloC₁-C₈alkyl, e.g. trifluoromethyl, C₅-C₁₀aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered

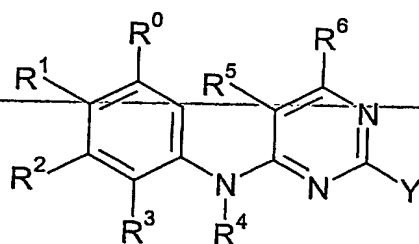
heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C₁-C₈alkoxy, e.g. methoxy, ethoxy or isopropoxy, haloC₁-C₈alkoxy, e.g. trifluoromethoxy, C₅-C₁₀aryloxy, e.g. phenoxy, unsubstituted or substituted heterocycloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC₁-C₈alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino or dimethylamino, halogen, e.g. fluoro or chloro, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl, or nitro; preferably hydrogen, methyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, trifluoromethoxy, phenoxy, 1-methyl-4-piperidyloxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 3-(N-methylpiperazino)-propoxy, methylamino, fluoro, chloro, sulfamoyl or nitro;

(j') R¹⁰ is C₁-C₈alkyl, e.g. methyl, ethyl or butyl, haloC₁-C₈alkyl, e.g. trifluoromethyl, C₁-C₈alkoxy, e.g. methoxy or ethoxy, unsubstituted or substituted heterocyclylC₁-C₈alkoxy, e.g. 2-(1-imidazolyl)ethoxy, unsubstituted or substituted amino, e.g. methylamino or dimethylamino, halogen, e.g. fluoro or chloro; preferably methyl, butyl, methoxy, ethoxy, 2-(1-imidazolyl)ethoxy, methylamino, dimethylamino or fluoro; and

(k') each pair of adjacent substituents R⁷ and R⁸, or R⁸ and R⁹ or R⁹ and R¹⁰, are -NH-CH=CH-, -CH=CH-NH-, -NH-N=CH-, -CH=N-NH-, -CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-, -O-CH₂-O-, or -O-CF₂-O-; preferably the pair of adjacent substituents R⁷ and R⁸ or R⁸ and R⁹ being -O-CH₂-O- or the pair of adjacent substituents R⁹ and R¹⁰ being -NH-CH=CH-, -CH=N-NH-, -CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂- or -O-CF₂-O-.

Most preferred as compounds of the formula I are those wherein the substituents have the meaning given in the Examples.

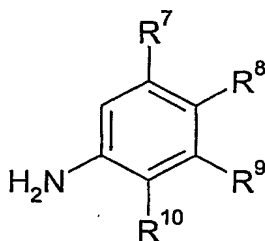
The present invention also provides a process for the production of a compound of formula I, comprising reacting a compound of formula II



(II)

wherein R^0 , R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are as defined above, and Y is a leaving group, preferably halogen such as bromide, iodine, or in particular chloride;

with a compound of formula III



(III)

wherein R^7 , R^8 , R^9 and R^{10} are as defined above;

and, if desired, converting a compound of formula I, wherein the substituents have the meaning as defined above, into another compound of formula I as defined;

and recovering the resulting compound of formula I in free form or as a salt, and, when required, converting the compound of formula I obtained in free form into the desired salt, or an obtained salt into the free form.

The reaction can be carried out in a manner known per se, the reaction conditions being dependent especially on the reactivity of the leaving group Y and the reactivity of the amino group in the aniline of formula III, usually in the presence of a suitable solvent or diluent or of a mixture thereof and, if necessary, in the presence of an acid or a base, with cooling or, preferably, with heating, for example in a temperature range from approximately -30°C to approximately $+150^{\circ}\text{C}$, especially approximately from 0°C to $+100^{\circ}\text{C}$, preferably from room temperature (approx. $+20^{\circ}\text{C}$) to $+80^{\circ}\text{C}$, in an open or closed reaction vessel and/or in the atmosphere of an inert gas, for example nitrogen.

If one or more other functional groups, for example carboxy, hydroxy or amino, are or need to be protected in a compound of formula II or III, because they should not take part in the reaction, these are such groups as are usually used in the synthesis of peptide compounds, cephalosporins and penicillins, as well as nucleic acid derivatives and sugars.

The protecting groups may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions, such as substitution reaction or solvolysis. It is a characteristic of protecting groups that they lend themselves readily, i.e. without undesired secondary reactions, to removal, typically by solvolysis, reduction, photolysis or also by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in the end-products. The specialist knows, or can easily establish, which protecting groups are suitable with the reactions mentioned hereinabove.

Salts of a compound of formula I with a salt-forming group may be prepared in a manner known per se. Acid addition salts of compounds of formula I may thus be obtained by treatment with an acid or with a suitable anion exchange reagent.

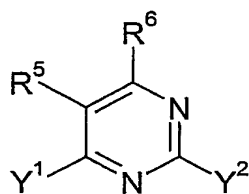
Salts can usually be converted to compounds in free form, e.g. by treating with suitable basic agents, for example with alkali metal carbonates, alkali metal hydrogencarbonates, or alkali metal hydroxides, typically potassium carbonate or sodium hydroxide.

Stereoisomeric mixtures, e.g. mixtures of diastereomers, can be separated into their corresponding isomers in a manner known per se by means of suitable separation methods. Diastereomeric mixtures for example may be separated into their individual diastereomers by means of fractionated crystallization, chromatography, solvent distribution, and similar procedures. This separation may take place either at the level of a starting compound or in a compound of formula I itself. Enantiomers may be separated through the formation of diastereomeric salts, for example by salt formation with an enantiomer-pure chiral acid, or by means of chromatography, for example by HPLC, using chromatographic substrates with chiral ligands.

It should be emphasized that reactions analogous to the conversions mentioned in this chapter may also take place at the level of appropriate intermediates.

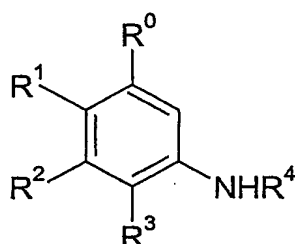
The compounds of formula I, including their salts, are also obtainable in the form of hydrates, or their crystals can include for example the solvent used for crystallization (present as solvates).

The compound of formula II used as starting materials may be obtained by reacting a compound of formula IV



(IV)

with a compound of formula V



(V)

wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as defined above, and Y^1 and Y^2 are identical or different leaving groups as defined above for Y. The reaction conditions are those mentioned above for the reaction of a compound of formula II with a compound of formula III.

The compounds of formula IV and V are known or may be produced in accordance with known procedures.

The compounds of formula I and their pharmaceutically acceptable salts exhibit valuable pharmacological properties when tested in vitro in cell-free kinase assays and in cellular assays, and are therefore useful as pharmaceuticals. In particular, the compounds of the invention are inhibitors of Focal Adhesion Kinase, and are useful as pharmaceuticals to treat conditions caused by a malfunction of signal cascades connected with Focal Adhesion Kinase, in particular tumors as described hereinbelow.

Focal Adhesion Kinase (FAK) is a key enzyme in the integrin-mediated outside-in signal cascade (D. Schlaepfer et al., Prog Biophys Mol Biol 1999, 71, 435-478). Interaction between cells and extracellular matrix (ECM) proteins is transduced as intracellular signals important for growth, survival and migration through cell surface receptors, integrins. FAK plays an essential role in these integrin-mediated outside-in signal cascades. The trigger in the signal transduction cascade is the autophosphorylation of Y397. Phosphorylated Y397 is a SH2 docking site for Src family tyrosine kinases. The bound c-Src kinase phosphorylates other tyrosine residues in FAK. Among them, phosphorylated Y925 becomes a binding site for the SH2 site of Grb2 small

adaptor protein. This direct binding of Grb2 to FAK is one of the key steps for the activation of down stream targets such as the Ras-ERK2/MAP kinase cascade.

The inhibition of endogenous FAK signalling results in reduced motility and in some cases induces cell death. On the other hand, enhancing FAK signalling by exogenous expression increases cell motility and transmitting a cell survival signal from ECM. In addition FAK is overexpressed in invasive and metastatic epithelial, mesenchymal, thyroid and prostate cancers. Consequently, an inhibitor of FAK is likely to be a drug for anti-tumor growth and metastasis. The compounds of the invention are thus indicated, for example, to prevent and/or treat a vertebrate and more particularly a mammal, affected by a neoplastic disease, in particular breast tumor, cancer of the bowel (colon and rectum), stomach cancer and cancer of the ovary and prostate, non-small cell lung cancer, small cell lung cancer, cancer of liver, melanoma, bladder tumor and cancer of head and neck.

The relation between FAK inhibition and immuno-system is described e.g. in G.A. van Seventer et al., Eur. J. Immunol. 2001, 31, 1417-1427. Therefore, the compounds of the invention are, for example, useful to prevent and/or treat a vertebrate and more particularly a mammal, affected by immune system disorders, diseases or disorders mediated by T lymphocytes, B lymphocytes, mast cells and/or eosinophils e.g. acute or chronic rejection of organ or tissue allo- or xenografts, atherosclerosis, vascular occlusion due to vascular injury such as angioplasty, restenosis, hypertension, heart failure, chronic obstructive pulmonary disease, CNS disease such as Alzheimer disease or amyotrophic lateral sclerosis, cancer, infectious disease such as AIDS, septic shock or adult respiratory distress syndrome, ischemia/reperfusion injury e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, or traumatic shock. The agent of the invention are also useful in the treatment and/or prevention of acute or chronic inflammatory diseases or disorders or autoimmune diseases e.g. rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, diabetes (type I and II) and the disorders associated with therewith, respiratory diseases such as asthma or inflammatory liver injury, inflammatory glomerular injury, cutaneous manifestations of immunologically-mediated disorders or illnesses, inflammatory and hyperproliferative skin diseases (such as psoriasis, atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis), inflammatory eye diseases, e.g. Sjogren's syndrome, keratoconjunctivitis or uveitis, inflammatory bowel disease, Crohn's disease or ulcerative colitis.

Compounds of the invention are active in a FAK assay system as described in the Examples, and show an inhibition IC_{50} in the range of 1 nM to 100 nM. Particularly active are the compounds Example No. 3-12 and No. 3-17 described hereinbelow showing IC_{50} values in the range of 1 to 5 nM.

Some of the compounds of the invention exhibit also ZAP-70 (zeta chain-associated protein of 70 kD) protein tyrosine kinase inhibiting activity. ZAP-70 protein tyrosine kinase interaction of the agents of the invention may be demonstrated by their ability to prevent phosphorylation of e.g. LAT-11 (linker for activation of T cell) by human ZAP-70 protein tyrosine kinase in aqueous solution, as described in the Examples. The compounds of the invention are thus also indicated for the prevention or treatment of disorders or diseases where ZAP-70 inhibition inhibition play a role.

Compounds of the invention are active in a ZAP-70 assay system as described in the Examples, and show an inhibition IC_{50} in the range of 1 μ M to 10 μ M, e.g. the compounds Example No. 2 and No. 3-2 described hereinbelow.

The compounds of the present invention also exhibit powerful inhibition of the tyrosine kinase activity of anaplastic lymphoma kinase (ALK) and the fusion protein of NPM-ALK. This protein tyrosine kinase results from a gene fusion of nucleophosmin (NPM) and the anaplastic lymphoma kinase (ALK), rendering the protein tyrosine kinase activity of ALK ligand-independent. NPM-ALK plays a key role in signal transmission in a number of hematopoietic and other human cells leading to hematological and neoplastic diseases, for example in anaplastic large-cell lymphoma (ALCL) and non-Hodgkin's lymphomas (NHL), specifically in ALK+ NHL or Alkomas, in inflammatory myofibroblastic tumors (IMT) and neuroblastomas. (Duyster J et al. 2001 Oncogene 20, 5623-5637). In addition to NPM-ALK, other gene fusions have been identified in human hematological and neoplastic diseases; mainly TPM3-ALK (a fusion of nonmuscle tropomyosin with ALK).

The inhibition of ALK tyrosine kinase activity can be demonstrated using known methods, for example using the recombinant kinase domain of the ALK in analogy to the VEGF-R kinase assay described in J. Wood et al. Cancer Res. 60, 2178-2189 (2000). In vitro enzyme assays using GST-ALK protein tyrosine kinase are performed in 96-well plates as a filter binding assay in 20 mM Tris-HCl, pH = 7.5, 3 mM $MgCl_2$, 10 mM $MnCl_2$, 1 mM DTT,

0.1 $\mu\text{Ci/assay}$ ($\approx 30 \mu\text{l}$) [$\gamma\text{-}^{33}\text{P}$]-ATP, 2 μM ATP, 3 $\mu\text{g/ml}$ poly (Glu, Tyr 4:1) Poly-EY (Sigma P-0275), 1 % DMSO, 25 ng ALK enzyme. Assays are incubated for 10 min at ambient temperature. Reactions are terminated by adding 50 μl of 125 mM EDTA, and the reaction mixture is transferred onto a MAIP Multiscreen plate (Millipore, Bedford, MA, USA), previously wet with methanol, and rehydrated for 5 min with H_2O . Following washing (0.5 % H_3PO_4), plates are counted in a liquid scintillation counter. IC_{50} values are calculated by linear regression analysis of the percentage inhibition. Compared with the control without inhibitor, the compounds of formula I inhibit the enzyme activity by 50 % (IC_{50}), for example in a concentration of from 0.001 to 0.5 μM , especially from 0.01 to 0.1 μM .

The compounds of formula I potentially inhibit the growth of human NPM-ALK overexpressing murine BaF3 cells (DSMZ Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Braunschweig, Germany). The expression of NPM-ALK is achieved by transfecting the BaF3 cell line with an expression vector pCIneoTM (Promega Corp., Madison WI, USA) coding for NPM-ALK and subsequent selection of G418 resistant cells. Non-transfected BaF3 cells depend on IL-3 for cell survival. In contrast NPM-ALK expressing BaF3 cells (named BaF3-NPM-ALK hereinafter) can proliferate in the absence of IL-3 because they obtain proliferative signal through NPM-ALK kinase. Putative inhibitors of the NPM-ALK kinase therefore abolish the growth signal and result in antiproliferative activity. The antiproliferative activity of putative inhibitors of the NPM-ALK kinase can however be overcome by addition of IL-3 which provides growth signals through an NPM-ALK independent mechanism. [For an analogous cell system using FLT3 kinase see E Weisberg et al. Cancer Cell; 1, 433-443 (2002)]. The inhibitory activity of the compounds of formula I is determined, briefly, as follows: BaF3-NPM-ALK cells (15,000/microtitre plate well) are transferred to 96-well microtitre plates. The test compounds [dissolved in dimethyl sulfoxide (DMSO)] are added in a series of concentrations (dilution series) in such a manner that the final concentration of DMSO is not greater than 1 % (v/v). After the addition, the plates are incubated for two days during which the control cultures without test compound are able to undergo two cell-division cycles. The growth of the BaF3-NPM-ALK cells is measured by means of YoproTM staining [T Idziorek et al. J. Immunol. Methods; 185: 249-258 (1995)]: 25 μl of lysis buffer consisting of 20 mM sodium citrate, pH 4.0, 26.8 mM sodium chloride, 0.4 % NP40, 20 mM EDTA and 20 mM is added to each well. Cell lysis is completed within 60 min at room temperature and total amount of Yopro bound to DNA is determined by measurement using the Cytofluor II 96-well reader (PerSeptive Biosystems) with the following settings: Excitation (nm) 485/20 and Emission (nm) 530/25.

IC₅₀ values are determined by a computer-aided system using the formula:

$$IC_{50} = [(ABS_{test} - ABS_{start}) / (ABS_{control} - ABS_{start})] \times 100. \text{ (ABS = absorption)}$$

The IC₅₀ value in those experiments is given as that concentration of the test compound in question that results in a cell count that is 50 % lower than that obtained using the control without inhibitor. The compounds of formula I exhibit inhibitory activity with an IC₅₀ in the range from approximately 0.01 to 1 µM.

The antiproliferative action of the compounds of formula I can also be determined in the human KARPAS-299 lymphoma cell line (DSMZ Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Braunschweig, Germany) [described in WG Dirks et al. Int. J. Cancer 100, 49-56 (2002)] using the same methodology described above for the BaF3-NPM-ALK cell line. The compounds of formula I exhibit inhibitory activity with an IC₅₀ in the range from approximately 0.01 to 1 µM.

The action of the compounds of formula I on autophosphorylation of the ALK can be determined in the human KARPAS-299 lymphoma cell line by means of an immunoblot as described in WG Dirks et al. Int. J. Cancer 100, 49-56 (2002). In that test the compounds of formula I exhibit an IC₅₀ of approximately from 0.001 to 1 µM.

Among the compounds of formula I, 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide is an especially potent ALK inhibitor, in that this compound inhibits the growth of the BaF3-NPM-ALK cells with an IC₅₀ of 97 nM. Further specifically preferred compounds that inhibit the tyrosine kinase activity of anaplastic lymphoma kinase (ALK) are the compounds described hereinafter in the examples 7A and 7B, as well as 7-2, 7-15, 7-36, 7-39, 7-44 and 7-52, respectively, all of which are having an IC₅₀ within the range from <0.5 to 200 nM.

For the above uses in the treatment of neoplastic diseases and immune system disorders the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.1 to about 100 mg/kg body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to

about 2000 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form.

The compounds of the invention may be administered by any conventional route, in particular parenterally, for example in the form of injectable solutions or suspensions, enterally, preferably orally, for example in the form of tablets or capsules, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Pharmaceutical compositions comprising a compound of the invention in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent. Unit dosage forms for oral administration contain, for example, from about 0.1 mg to about 500 mg of active substance. Topical administration is e.g. to the skin. A further form of topical administration is to the eye.

The pharmaceutical compositions of the present invention are prepared in a manner known per se, for example by means of conventional mixing, granulating, coating, dissolving or lyophilizing processes.

Preference is given to the use of solutions of the active ingredient, and also suspensions or dispersions, especially isotonic aqueous solutions, dispersions or suspensions which, for example in the case of lyophilized compositions comprising the active ingredient alone or together with a carrier, for example mannitol, can be made up before use. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers and are prepared in a manner known per se, for example by means of conventional dissolving and lyophilizing processes. The said solutions or suspensions may comprise viscosity-increasing agents, typically sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone, or gelatins, or also solubilizers, e.g. Tween 80® (polyoxyethylene(20)sorbitan mono-oleate).

Suspensions in oil comprise as the oil component the vegetable, synthetic, or semi-synthetic oils customary for injection purposes. In respect of such, special mention may be made of liquid fatty acid esters that contain as the acid component a long-chained fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms, for example lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or

corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brassidic acid or linoleic acid, if desired with the addition of antioxidants, for example vitamin E, β -carotene or 3,5-di-tert-butyl-4-hydroxytoluene. The alcohol component of these fatty acid esters has a maximum of 6 carbon atoms and is a monovalent or polyvalent, for example a mono-, di- or trivalent, alcohol, for example methanol, ethanol, propanol, butanol or pentanol or the isomers thereof, but especially glycol and glycerol. As fatty acid esters, therefore, the following are mentioned: ethyl oleate, isopropyl myristate, isopropyl palmitate, "Labrafil M 2375" (polyoxyethylene glycerol), "Labrafil M 1944 CS" (unsaturated polyglycolized glycerides prepared by alcoholysis of apricot kernel oil and consisting of glycerides and polyethylene glycol ester), "Labrasol" (saturated polyglycolized glycerides prepared by alcoholysis of TCM and consisting of glycerides and polyethylene glycol ester; all available from Gattefossé, France), and/or "Miglyol 812" (triglyceride of saturated fatty acids of chain length C_8 to C_{12} from Hüls AG, Germany), but especially vegetable oils such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and more especially groundnut oil.

The manufacture of injectable preparations is usually carried out under sterile conditions, as is the filling, for example, into ampoules or vials, and the sealing of the containers.

Pharmaceutical compositions for oral administration can be obtained, for example, by combining the active ingredient with one or more solid carriers, if desired granulating a resulting mixture, and processing the mixture or granules, if desired or necessary, by the inclusion of additional excipients, to form tablets or tablet cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations, and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

Tablet cores can be provided with suitable, optionally enteric, coatings through the use of, inter alia, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or tablet coatings, for example for identification purposes or to indicate different doses of active ingredient.

Pharmaceutical compositions for oral administration also include hard capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticizer, such as glycerol or sorbitol. The hard capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders, and/or glidants, such as talc or magnesium stearate, and optionally stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols or fatty acid esters of ethylene or propylene glycol, to which stabilizers and detergents, for example of the polyoxyethylene sorbitan fatty acid ester type, may also be added.

Pharmaceutical compositions suitable for rectal administration are, for example, suppositories that consist of a combination of the active ingredient and a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

For parenteral administration, aqueous solutions of an active ingredient in water-soluble form, for example of a water-soluble salt, or aqueous injection suspensions that contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, stabilizers, are especially suitable. The active ingredient, optionally together with excipients, can also be in the form of a lyophilizate and can be made into a solution before parenteral administration by the addition of suitable solvents.

Solutions such as are used, for example, for parenteral administration can also be employed as infusion solutions.

Preferred preservatives are, for example, antioxidants, such as ascorbic acid, or microbicides, such as sorbic acid or benzoic acid.

The compounds of the invention may be administered as the sole active ingredient or together with other drugs useful against neoplastic diseases or useful in immunomodulating regimens. For example, the agents of the invention may be used in accordance with the invention in combination with pharmaceutical compositions effective in various diseases as described above, e.g. with cyclophosphamide, 5-fluorouracil, fludarabine, gemcitabine, cisplatin, carboplatin, vincristine, vinblastine, etoposide, irinotecan, paclitaxel, docetaxel, rituxan, doxorubicine, gefitinib, or imatinib; or also with cyclosporins, rapamycins, ascomycins or their immunosuppressive analogs, e.g. cyclosporin A, cyclosporin G, FK-506, sirolimus or everolimus, corticosteroids, e.g. prednisone, cyclophosphamide, azathioprene, methotrexate, gold salts, sulfasalazine, antimalarials, brequinar, leflunomide, mizoribine, mycophenolic acid, mycophenolate, mofetil, 15-deoxyspergualine, immuno-suppressive monoclonal antibodies, e.g. monoclonal antibodies to leukocyte receptors, e.g. MHC, CD2, CD3, CD4, CD7, CD25, CD28, CD40, CD45, CD58, CD80, CD86, CD152, CD137, CD154, ICOS, LFA-1, VLA-4 or their ligands, or other immunomodulatory compounds, e.g. CTLA4Ig.

In accordance with the foregoing, the present invention also provides:

- (1) A compound of the invention for use as a pharmaceutical;
- (2) a compound of the invention for use as a FAK inhibitor, an ALK inhibitor and/or ZAP-70 inhibitor, for example for use in any of the particular indications hereinbefore set forth;
- (3) a pharmaceutical composition, e.g. for use in any of the indications herein before set forth, comprising a compound of the invention as active ingredient together with one or more pharmaceutically acceptable diluents or carriers;
- (4) a method for the treatment of any particular indication set forth hereinbefore in a subject in need thereof which comprises administering an effective amount of a compound of the invention or a pharmaceutical composition comprising same;
- (5) the use of a compound of the invention for the manufacture of a medicament for the treatment or prevention of a disease or condition in which FAK, ALK and/or ZAP-70 activation plays a role or is implicated;
- (6) the method as defined above under (4) comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a compound of the invention and one or

- more further drug substances, said further drug substance being useful in any of the particular indications set forth hereinbefore;
- (7) a combination comprising a therapeutically effective amount of a compound of the invention and one or more further drug substances, said further drug substance being useful in any of the particular indications set forth hereinbefore;
- (8) use of a compound of the invention for the manufacture of a medicament for the treatment or prevention of a disease which responds to inhibition of the anaplastic lymphoma kinase;
- (9) the use according to (8), wherein the disease to be treated is selected from anaplastic large-cell lymphoma, non-Hodgkin's lymphomas, inflammatory myofibroblastic tumors and neuroblastomas;
- (10) the use according to (8) or (9), wherein the compound is 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide or a pharmaceutically acceptable salt thereof, or any of the the compounds described hereinafter in the examples 7A and 7B, as well as 7-2, 7-15, 7-36, 7-39, 7-44 and 7-52 or a pharmaceutically acceptable salt of any one of these;
- (11) a method for the treatment of a disease which responds to inhibition of the anaplastic lymphoma kinase, especially a disease selected from anaplastic large-cell lymphoma, non-Hodgkin's lymphomas, inflammatory myofibroblastic tumors and neuroblastomas, comprising administering an effective amount of a compound of the invention, especially 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide, or a pharmaceutically acceptable salt thereof.

The following Examples serve to illustrate the invention without limiting the invention in its scope.

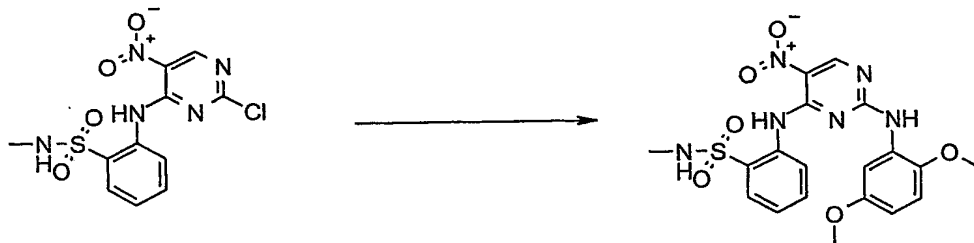
Examples

Abbreviations

AcOH = acetic acid, ALK = anaplastic lymphoma kinase, ATP = adenosine 5'-triphosphate, brine = saturated sodium chloride solution, BSA = bovine serum albumin, DIAD = diisopropyl azodicarboxylate, DIPCDI = N,N'-diisopropylcarbodiimid, DMAP = 4-dimethylaminopyridine, DMF = N,N-dimethylformamide, DTT = 1,4-dithio-D,L-threitol, EDTA = ethylene diamine tetraacetic acid, Et = ethyl, EtOAc = ethyl acetate, EtOH = ethanol, Eu-PT66 = LANCE™ europium-W1024-labelled anti-phosphotyrosine antibody (Perkin Elmer), FAK = Focal Adhesion

Kinase, FRET = fluorescence resonance energy transfer, HEPES = N-2-hydroxyethyl-piperazine-N'-2-ethanesulfonic acid, HOAt = 1-hydroxy-7-azabenzotriazole, Me = methyl, RT-PCR = reverse transcription polymerase chain reaction, SA-(SL)APC = Streptavidin conjugated to SuperLight™ allophycocyanin (Perkin Elmer), subst. = substituted, TBTU = O-(benzotriazol-1-yl)-N,N,N',N'-tetramethylammonium tetrafluoroborate, THF = tetrahydrofuran.

Example 1: 2-[2-(2,5-Dimethoxy-phenylamino)-5-nitro-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide



To a solution of 2-(2-chloro-5-nitro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide (100 mg, 0.29 mmol) in EtOH (3 mL), 2,5-dimethoxyaniline (49 mg, 0.32 mmol) is added at room temperature. The mixture is heated at 78°C for 5 h. The solvent is evaporated, and the mixture is purified by reverse phase HPLC to give the title product in.

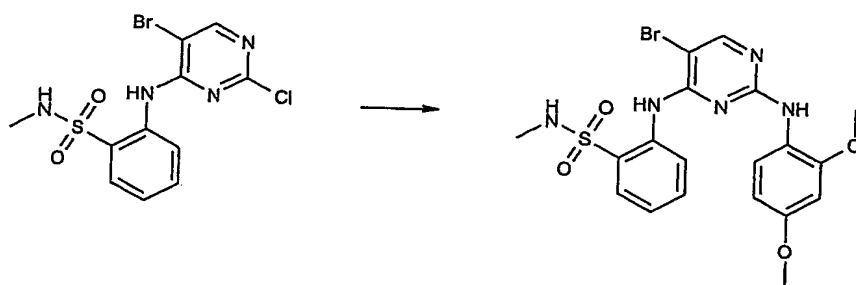
R_f = 0.47 (n-hexane : ethyl acetate = 1:1). ¹H-NMR (400 MHz, CDCl₃), δ (ppm): 2.36 (d, 3H), 3.57 (s, 3H), 3.73 (s, 3H), 6.72 (d, 1H), 6.99 (d, 1H), 7.17 (s, 1H), 7.35 (t, 1H), 7.4-7.6 (m, 1H), 7.63 (d, 1H), 7.81 (d, 1H), 8.0-8.2 (m, 1H), 9.13 (s, 1H), 9.41 (br.s, 1H), 11.0 (s, 1H).

Preparation of 2-(2-chloro-5-nitro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide:

2,4-Dichloro-5-nitro-pyrimidine (1.94 g, 10 mmol) and 2-amino-N-methyl-benzenesulfonamide (1.86 g, 10 mmol) are dissolved in CHCl₃ (30 mL). The reaction mixture is heated at 61°C for 2 h. The solvent is evaporated and the residue is washed with ether to give the title product.

R_f = 0.5 (n-hexane : ethyl acetate = 1:1). ¹H-NMR (400MHz, CDCl₃), δ (ppm): 2.67 (d, 3H), 4.6-4.7 (m, 2H), 7.41 (t, 1H), 7.7 (t, 1H), 8.04 (d, 1H), 8.15 (d, 1H), 9.21 (s, 1H), 11.2 (s, 1H).

Example 2: 2-[5-Bromo-2-(2,4-dimethoxy-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide



To a solution of 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide (300 mg, 0.79 mmol), 2,4-dimethoxyaniline (181.5 mg, 1.18 mmol) in ethanol (3 mL), 1 N hydrochloric acid (0.03 mL) is added and stirred under reflux condition for 5 hours. The reaction mixture is cooled to room temperature, poured into water and extracted twice with ethyl acetate. The organic layer is successively washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane : ethyl acetate = 5:1 to 1:1) to afford the title compound.

$^1\text{H-NMR}$ (CDCl_3), δ (ppm): 8.95 (s, 1H), 8.44 (d, 1H), 8.20 (s, 1H), 7.98 (dd, 1H), 7.58 (dt, 1H), 7.22-7.32 (m, 1H), 6.51 (d, 1H), 6.40 (d, 1H), 4.56-4.48 (m, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 2.64 (d, 3H). R_f (n-hexane : ethyl acetate = 1:1): 0.31.

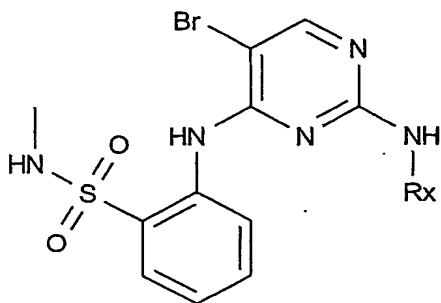
Preparation of 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide

A solution of 5-bromo-2,4-dichloropyrimidine (684 mg, 3.0 mmol) and 2-amino-N-methyl-benzenesulfonamide (559 mg, 3.0 mmol) in N,N-dimethylformamide (10 mL) containing potassium carbonate (830 mg, 6.0 mmol) is stirred at room temperature for 23 hours. Saturated aqueous ammonium chloride is added and the mixture is poured into water and extracted twice with ethyl acetate. The organic layer is washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane - ethyl acetate gradient) to afford the title compound as a slightly yellow solid.

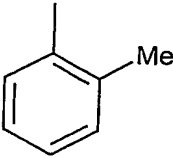
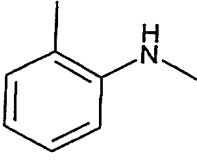
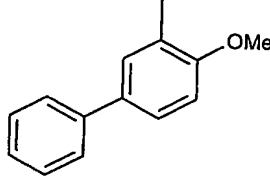
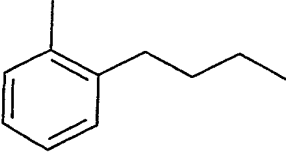
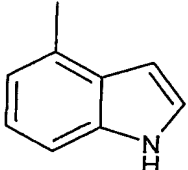
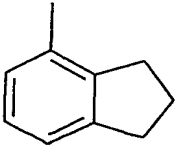
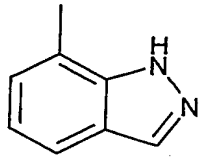
$^1\text{H-NMR}$ (CDCl_3), δ (ppm): 2.67 (d, 3H), 4.79 (q, 1H), 7.26 (s, 1H), 7.29 (ddd, 1H), 7.66 (ddd, 1H), 7.95 (dd, 1H), 8.37 (s, 1H), 8.48 (d, 1H), 9.52 (s, 1H). R_f (n-hexane : ethyl acetate = 10:3): 0.33.

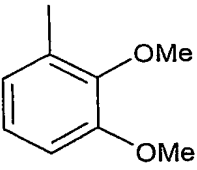
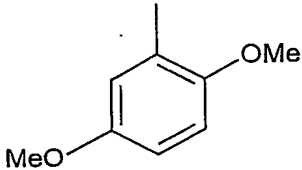
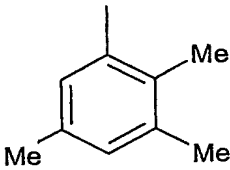
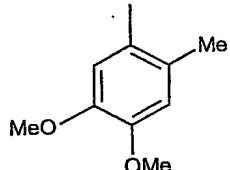
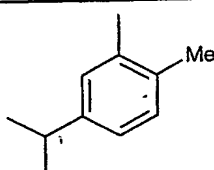
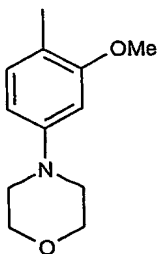
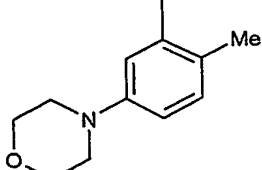
Example 3:

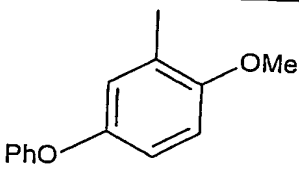
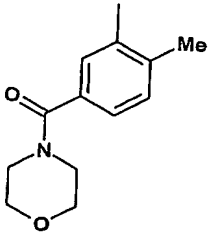
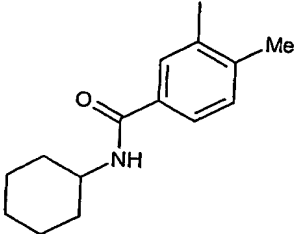
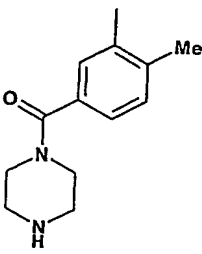
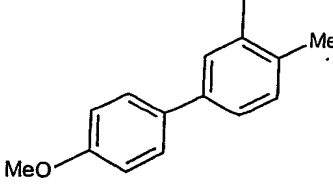
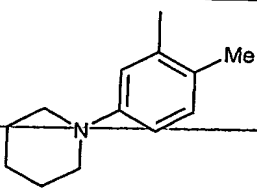
The following 2-[5-bromo-2-(subst. phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamides were prepared from 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide and the corresponding aniline following the procedure of Example 2:



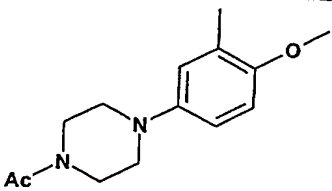
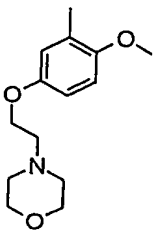
Expl No.	Rx	Rf (solvent)	NMR (400MHz) in CDCl ₃ , δ (ppm)
3-1		0.48 (<i>n</i> -hexane: AcOEt=1:1)	2.64(d, 3H), 4.48-4.40(m, 1H), 6.78(d, 1H), 6.87(bs, 1H), 6.99(dd, 1H), 6.82(s, 1H), 7.54(dt, 1H), 7.79(d, 1H), 7.97(dd, 1H), 8.28(s, 1H), 8.32(dd, 1H), 9.07(s, 1H)
3-2		0.58 (<i>n</i> -hexane: AcOEt=1:1)	2.25(s, 3H), 2.33(s, 3H), 2.63(d, 3H), 4.53-4.45(m, 1H), 6.61(bs, 1H), 6.99(dd, 1H), 7.04(s, 1H), 7.18(dt, 1H), 7.43(dt, 1H), 7.56(d, 1H), 7.92(dd, 1H), 8.19(s, 1H), 8.41(dd, 1H), 9.08(s, 1H)
3-3		0.36 (<i>n</i> -hexane: AcOEt=1:1)	2.23(s, 3H), 2.62(d, 3H), 3.69(s, 3H), 4.53-4.44(m, 1H), 6.62(dd, 1H), 6.69(bs, 1H), 7.10(d, 1H), 7.19(t, 1H), 7.48(d, 1H), 7.51(dd, 1H), 7.93(dd, 1H), 8.22(s, 1H), 8.44(dd, 1H), 9.09(s, 1H)
3-4		0.41 (<i>n</i> -hexane: AcOEt=1:1)	2.32(s, 3H), 2.63(d, 3H), 4.45-4.44(bm, 1H), 6.85(d, 1H), 6.91(d, 1H), 7.00(bs, 1H), 7.28-7.24(m, 1H), 7.57(t, 1H), 7.99(dd, 1H), 8.25(s, 1H), 8.39(d, 1H), 9.00(bs, 1H)
3-5		0.39 (<i>n</i> -hexane: AcOEt=1:1)	2.33(s, 3H), 2.63(d, 3H), 3.87(s, 3H), 4.46-4.44(bm, 1H), 6.66(d, 1H), 6.71(s, 1H), 7.48(bs, 1H), 7.63-7.59(m, 1H), 7.97(dd, 1H), 8.05(d, 1H), 8.23(s, 1H), 8.44(d, 1H), 8.92(bs, 1H)
3-6		0.27 (<i>n</i> -hexane: AcOEt=3:1)	2.63(d, 3H), 3.90(s, 3H), 4.45-4.40(bm, 1H), 6.90-6.86(m, 2H), 7.00-6.96(m, 1H), 7.23-7.17(m, 3H), 7.45(t, 1H), 6.4-7.60(m, 2H), 7.97(dd, 1H), 8.22(d, 1H), 8.26(s, 1H), 8.43(d, 1H), 8.94(bs, 1H)

3-7		0.34 (<i>n</i> -hexane: AcOEt=3:1)	2.30(s, 3H), 2.63(d, 3H), 4.44-4.43(bm, 1H), 6.68 (bs, 1H), 7.00-6.68(m, 1H), 7.23-7.17(m, 2H), 7.46-7.43(m, 1H), 7.76(d, 1H), 7.93(dd, 1H), 8.22 (s, 1H), 8.40(d, 1H), 9.01(bs, 1H)
3-8		0.12 (<i>n</i> -hexane: AcOEt=3:1)	2.62(d, 3H), 2.81(s, 3H), 4.07-3.98(m, 1H), 4.52-4.45(bm, 1H), 6.37(bs, 1H), 6.77-6.73 (m, 2H), 7.12(t, 1H), 7.24-7.20(m, 1H), 7.30-7.27(m, 1H), 7.35(t, 1H), 7.88(dd, 1H), 8.18 (s, 1H), 8.41(d, 1H), 9.19(bs, 1H)
3-9		0.28 (<i>n</i> -hexane: AcOEt=3:1)	2.62(d, 3H), 3.94(s, 3H), 4.49-4.43(bm, 1H), 6.99-6.90 (m, 3H), 7.18-7.23(m, 1H), 7.31-7.24(m, 3H), 7.63(bs, 1H), 7.93-7.86(m, 1H), 8.28-8.23(m, 1H), 8.28 (s, 1H), 8.45(bs, 1H), 8.89(bs, 1H)
3-10		0.23 (<i>n</i> -hexane: AcOEt=3:1)	0.91(t, 3H), 1.37 (dd, 2H), 1.64-1.55 (m, 2H), 2.64-2.60 (m, 2H), 4.45-4.40 (bm, 1H), 6.69 (bs, 1H), 7.23-7.10(m, 1H), 7.46-7.38 (m, 1H), 7.73 (d 1H), 7.92 (d, 1H), 8.21 (s, 1H), 8.38-8.46 (m, 1H), 9.09 (bs, 1H)
3-11		0.12 (<i>n</i> -hexane: AcOEt=3:1)	2.63 (d, 3H), 4.15-4.10 (bm, 1H), 6.58 (bs, 1H), 7.31-7.10(m, 4H), 7.53-7.49 (m, 1H), 7.71(d 1H), 7.95 (d, 1H), 8.30-8.23 (bm, 1H), 8.26 (s, 1H), 8.45 (d, 1H), 9.03 (bs, 1H)
3-12		0.4 (<i>n</i> -hexane: AcOEt=3:1)	2.09 (dd, 2H), 2.63 (d, 3H), 2.85(t, 2H), 2.96 (t, 2H), 4.46-4.43 (m, 2H), 6.73 (bs, 1H), 6.99 (d, 1H), 7.09 (t, 1H), 7.25-7.20(m, 1H), 7.52 (t, 1H), 7.74 (d 1H), 7.92 (dd, 1H), 8.22 (s, 1H), 8.42 (d, 1H), 9.02 (bs, 1H)
3-13		0.33 (AcOEt)	2.63 (d, 3H), 4.63-4.64 (bm, 1H), 7.11(d, 2H), 7.18(t, 1H), 7.42-7.34(bm, 1H), 7.58-7.55(m, 1H), 7.96(d, 1H), 8.07(s, 1H), 8.19-8.10(bm, 1H), 8.24(s, 1H), 9.15(s, 1H), 11.6-11.4(bm, 1H)

3-14		0.28 (<i>n</i> -hexane: AcOEt=3:1)	2.63(d, 3H), 3.88(s, 3H), 3.89(s, 3H), 4.47-4.41(m, 1H), 6.60(d, 1H), 6.92 (t, 1H), 7.64 (dd, 1H), 7.66-7.61(m, 1H), 7.89(d, 1H), 7.98(dd, 1H), 8.26(s, 1H), 8.43(d, 1H), 8.95(s, 1H)
3-15		0.30 (<i>n</i> -hexane: AcOEt=3:1)	2.63(d, 3H), 3.66(s, 3H), 3.85(s, 3H), 4.45-4.44(m, 1H), 6.48(dd, 1H), 6.79(d, 1H), 7.64(dd, 1H), 7.97(dd, 2H), 8.26(s, 1H), 8.44(d, 1H), 8.96(s, 1H)
3-16		0.22 (<i>n</i> -hexane: AcOEt=3:1)	2.17(s, 3H), 2.22(s, 3H), 2.64(s, 3H), 2.63(d, 3H), 4.46-4.44(m, 1H), 6.57(bs, 1H), 7.00(s, 1H), 7.17(t, 1H), 7.44-7.40(m, 1H), 7.44(s, 1H), 7.93(dd, 1H), 8.19(s, 1H), 8.43(d, 1H), 9.06(s, 1H)
3-17		0.46 (AcOEt)	2.22(s, 3H), 2.63(d, 3H), 3.68(s, 3H), 3.89(s, 3H), 4.52-4.47(m, 1H), 6.51(s, 1H), 6.74(s, 1H), 7.12(s, 1H), 7.16-7.12(m, 1H), 7.40(t, 1H), 7.91(dd, 1H), 8.19(s, 1H), 8.42(d, 1H), 9.12(s, 1H)
3-18		0.35 (<i>n</i> -hexane: AcOEt=3:1)	1.16(d, 6H), 2.25 (s, 3H), 2.62(d, 3H), 2.77(t, 1H), 4.49-4.48(m, 1H), 7.00(s, 1H), 7.15(d, 1H), 7.41-7.37(m, 1H), 7.49(d, 2H), 7.54(dd, 1H), 7.92(dd, 1H), 8.21(s, 1H), 8.32(d, 1H), 9.02(s, 1H)
3-19		0.23 (<i>n</i> -hexane: AcOEt=1:1)	2.63(d, 3H), 3.13-3.10 (m, 4H), 3.87(s, 3H), 3.89-3.86(m, 4H), 4.97-4.93(m, 1H), 6.41(dd, 1H), 6.52(d, 1H), 7.24-7.22(m, 1H), 7.32(s, 1H), 7.57(t, 1H), 7.96(dd, 1H), 8.01(d, 1H), 8.14(s, 1H), 8.44(d, 1H), 8.98 (s, 1H)
3-20		0.36 (<i>n</i> -hexane: AcOEt=1:1)	2.22(s, 3H), 2.64(d, 3H), 3.00-3.2.97 (m, 4H), 3.76-3.74(m, 4H), 4.54-4.50(m, 1H), 6.64(d, 1H), 6.66(t, 1H), 7.11(d, 1H), 7.18(t, 1H), 7.37(d, 1H), 7.46(t, 1H), 7.93(dd, 1H), 8.22(s, 1H), 8.42(d, 1H), 9.09 (s, 1H)

3-21		0.25 (<i>n</i> -hexane: AcOEt=3:1)	2.52(d, 3H), 3.90(s, 3H), 4.36-4.32(m, 1H), 6.60(dd, 1H), 6.84(t, 3H), 7.02-6.98(m, 1H), 7.10(t, 1H), 7.31-7.24(m, 1H), 7.38-7.34(m, 1H), 7.72(s, 1H), 7.87(dd, 1H), 8.11(d, 1H), 8.23(s, 1H), 8.26-8.23(m, 1H), 8.83(s, 1H)
3-22		0.27 (AcOEt)	2.33(s, 3H), 2.65(d, 3H), 3.60-3.45(bm, 8H), 4.53-4.49(m, 1H), 6.74(s, 1H), 7.11(d, 1H), 7.22-7.18(m, 1H), 7.58-7.54(m, 1H), 7.94(dd, 1H), 8.00(d, 1H), 8.22(s, 1H), 8.37(d, 1H), 9.13(s, 1H)
3-23		0.38 (AcOEt)	1.24-1.08(m, 2H), 1.46-1.32(m, 2H), 1.76-1.67(m, 2H), 1.98-1.90(m, 2H), 2.33(s, 3H), 2.64(d, 3H), 3.95-3.90(m, 1H), 4.49-4.47(m, 1H), 5.89-5.80(bm, 1H), 6.66(s, 1H), 7.15(t, 1H), 7.48-7.31(m, 2H), 7.91(dd, 1H), 8.12(s, 1H), 8.23(s, 1H), 8.41(d, 1H), 9.18(s, 1H)
3-24		0.11 (AcOEt)	2.35(s, 3H), 2.71(s, 3H), 3.07-2.73(m, 2H), 3.86-3.31(m, 6H), 6.85(s, 1H), 7.10(d, 1H), 7.24-7.19(m, 1H), 7.52-7.48(m, 1H), 7.66-7.59(m, 2H), 7.93(d, 1H), 8.06(s, 1H), 8.27-8.21(m, 1H), 8.23(s, 1H), 9.11(s, 1H)
3-25		0.5 (<i>n</i> -hexane: AcOEt=1:1)	2.52(d, 3H), 2.62(s, 3H), 4.36-4.32(m, 1H), 6.74(s, 1H), 6.87(d, 2H), 7.00-6.91(m, 2H), 7.00-6.97(m, 2H), 7.38(dd, 2H), 7.86(dd, 1H), 7.98(s, 1H), 8.23(s, 1H), 8.28(d, 1H), 9.04(s, 1H)
3-26		0.45 (<i>n</i> -hexane: AcOEt=1:1)	1.62-1.34(m, 6H), 2.13(s, 3H), 2.56(d, 3H), 3.01-2.87(m, 4H), 4.54-4.38(m, 1H), 6.59(s, 1H), 6.69-6.59(bm, 1H), 7.02(d, 1H), 7.10-7.07(m, 1H), 7.37(t, 1H), 7.84(dd, 1H), 8.15(s, 1H), 8.34(d, 1H), 9.01(s, 1H)

3-27		0.45 (<i>n</i> -hexane: AcOEt=1:1)	2.32(s, 3H), 2.58(d, 3H), 3.75(s, 3H), 4.37-4.44(m, 1H), 6.77-6.73(m, 1H), 6.89-6.82(m, 1H), 6.97-6.91(m, 2H), 6.96(d, 1H), 7.20(dd, 1H), 7.25-7.24(m, 1H), 7.33-7.29(m, 1H),
3-28		0.35 (<i>n</i> -hexane: AcOEt=1:1)	2.34(s, 3H), 2.64(d, 3H), 3.81(s, 3H), 4.57-4.50(m, 1H), 6.76(bs, 1H), 6.91-6.84(m, 4H), 7.04(d, 1H), 7.83(dd, 1H), 8.06(d, 1H), 8.19(dd, 1H), 8.23(s, 1H), 9.00(s, 1H)
3-29		0.45 (<i>n</i> -hexane: AcOEt=1:1)	1.50(t, 3H), 2.62 (d, 3H), 4.17(dd, 2H), 4.51-4.44(m, 1H), 6.95-6.89 (m, 2H), 6.94(d, 1H), 7.16 (dd, 1H), 7.31-7.23(m, 5H), 7.67(s, 1H), 7.11(dd, 1H), 7.23(d, 2H), 7.65(s, 1H), 7.88(dd, 1H), 8.28-8.23(m, 1H), 8.28(s, 1H), 8.43(s, 1H), 8.89(s, 1H)
3-30		0.45 (<i>n</i> -hexane: AcOEt=1:1)	1.49(t, 3H), 2.63(d, 3H), 3.85(s, 3H), 4.16(dd, 2H), 4.55-4.48(m, 1H), 6.81(dd, 1H), 6.95-6.91(m, 3H), 7.11(dd, 1H), 7.23(d, 2H), 7.65(s, 1H), 7.90-7.88(m, 1H), 8.28-8.26(m, 1H), 8.27(s, 1H), 8.39(s, 1H), 8.90(s, 1H)
3-31		0.29 (<i>n</i> -hexane: AcOEt=1:1)	¹ H-NMR : (CDCl ₃) 1.83-1.72 (4H, m), 2.63 (3H, d), 2.66-2.62 (2H, m), 2.80 (2H, t), 4.41-4.44 (1H, m), 6.64 (1H, br.s), 6.92 (1H, d), 7.09 (1H, t), 7.18 (1H, t), 7.45 (1H, t), 7.59 (1H, t), 7.92 (1H, d), 8.20 (1H, s), 8.42 (1H, d), 9.08 (1H, br.s).
3-32		0.3 (<i>n</i> -hexane: AcOEt=1:1)	DMSO-d ₆ : 2.43(s, 3H), 2.80-2.82(m, 4H), 3.61-3.64 (m, 4H), 3.75(s, 3H), 6.62(dd, 1H), 6.93(d, 1H), 7.46(d, 1H), 7.54(dd, 1H), 7.77(dd, 2H), 8.14(bs, 1H), 8.32(s, 1H), 8.38-8.30(m, 1H), 9.14(bs, 1H)
3-33		0.61 (MeOH: CH ₂ Cl ₂ =1: 1)	DMSO-d ₆ : 1.59-1.68(m, 2H), 1.88-1.98(m, 2H), 2.13-2.25(m, 2H), 2.19(s, 3H), 2.43(s, 3H), 2.60-2.70(m, 2H), 3.75(s, 3H), 4.32-4.40(m, 1H), 6.51(dd, 1H), 6.64(d, 1H), 7.20(dd, 1H), 7.39(d, 1H), 7.75(dd, 1H), 7.70-7.78(s, 1H), 8.22(s, 1H), 8.26(s, 1H), 8.38-

			8.41(m, 1H), 9.22(s, 1H)
3-34		0.17 (AcOEt)	CDCl ₃ : 2.11(s, 3H), 2.68(d, 3H), 2.76-2.83(m, 2H), 2.89-2.97(m, 2H), 3.47-3.55(m, 2H), 3.58-3.66(m, 2H), 3.86(s, 3H), 4.70-4.78(m, 1H), 6.53(dd, 1H), 6.81(d, 1H), 7.23(dd, 1H), 7.54-7.62(m, 2H), 7.97(dd, 1H), 8.02-8.03(m, 1H), 8.29(s, 1H), 8.40(d, 1H), 8.99(bs, 1H)
3-35		0.22 (AcOEt only)	DMSO-d ₆ : 2.40-2.48(m, 7H), 2.63(t, 2H), 3.50-3.58(m, 4H), 3.77(s, 3H), 3.91(t, 2H), 6.60(dd, 1H), 6.93(d, 1H), 7.28(dd, 1H), 7.56(d, 1H), 7.60(dd, 1H), 7.75-7.80(m, 1H), 7.80(dd, 1H), 8.10(s, 1H), 8.35(s, 1H), 8.40(d, 1H), 9.21(s, 1H)

Example 4: 2-[5-Bromo-2-(subst. phenylamino)-pyrimidin-4-ylamino]-N-propyl-benzene-sulfonamides

These compounds are prepared in analogy to Example 2 using 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-propyl-benzenesulfonamide and the corresponding aniline to give compounds No. 4-1 to 4-31 having the substituent Rx as listed under Example 3 for compounds No. 3-1 to 3-31.

Preparation of 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-propyl-benzenesulfonamide

To a solution of 5-bromo-2,4-dichloropyrimidine (90 μ L, 0.70 mmol) and 2-amino-N-propyl-benzenesulfonamide (100 mg, 0.47 mmol), sodium hydride (54.2 mg, 0.56 mmol) in DMSO (1.0 mL) is added and the resulting solution is stirred at 80°C for 3.0 h. The mixture is poured into water and extracted with ethyl acetate three times. The organic layer is washed with water and then brine, dried over sodium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1) to afford the title compound as a slightly yellow solid.

¹H-NMR (δ , ppm) : 0.89 (t, 3H), 1.41 (q, 2H), 3.56 (t, 2H), 4.92 (br.s, 2H), 6.71 (dd, 1H), 6.77 (t, 1H), 7.33 (t, 1H), 7.54 (dd, 1H), 8.79 (s, 1H)

R_f (hexane : ethyl acetate = 1:1): 0.64.

Example 5: 2-[5-Trifluoromethyl-2-(subst. phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamides

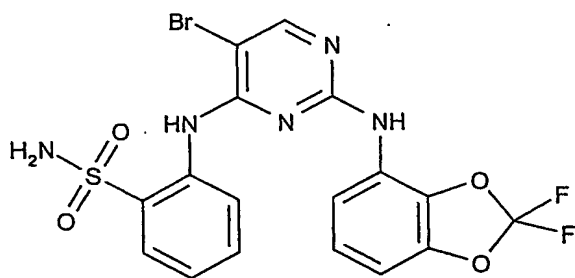
These compounds are prepared in analogy to Example 2 using 2-(2-chloro-5-trifluoromethyl-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide and the corresponding aniline to give compounds No. 5-1 to 5-31 having the substituent Rx as listed under Example 3 for compounds No. 3-1 to 3-31.

Preparation of 2-(2-chloro-5-trifluoromethyl-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide

To a solution of 2,4-dichloro-5-trifluoromethyl-pyrimidine (386 mg, 1.79 mmol) in acetonitrile (10 mL), 2-amino-N-methyl-benzenesulfonamide (333 mg, 1.79 mmol) and 1,8-diaza[5.4.0]-bicyclo-7-undecene (280 μ L, 1.88 mmol) are added successively at ambient temperature. After stirring for 15 h at room temperature, dichloromethane (30 mL) is added to the mixture, and the solution is washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated in vacuo. The resulting solid is purified by flash chromatography.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.73(s, 3H), 6.67-6.69(m, 1H), 6.72-6.73(m, 1H), 7.27-7.31(m, 1H), 7.78(dd, 1H), 8.60(s, 1H). R_f (hexane : ethyl acetate = 1:1): 0.28.

Example 6: 2-[5-Bromo-2-(2,3-[difluoromethylenedioxy]phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide



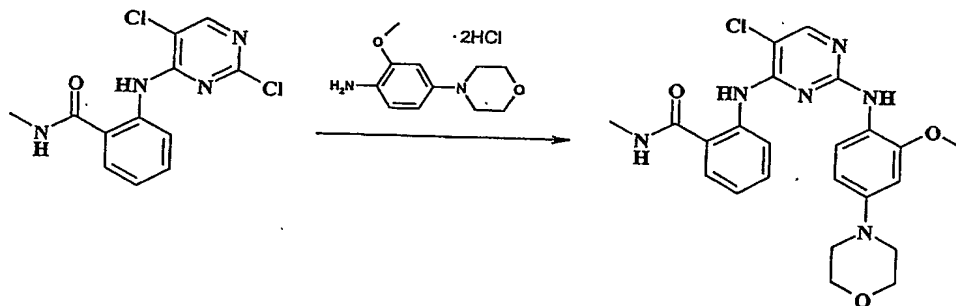
This compound was obtained as a side product formed by N-demethylation on reaction of 2-(5-bromo-2-chloropyrimidin-4-ylamino)-N-methyl-benzenesulfonamide with 2,3-(difluoromethylenedioxy)aniline following the procedure of Example 2. It may also be prepared by reaction of 2-(5-bromo-2-chloropyrimidin-4-ylamino)benzenesulfonamide with 2,3-(difluoromethylenedioxy)-aniline.

R_f (*n*-hexane: ethyl acetate = 1:1): 0.46.

$^1\text{H-NMR}$: (CDCl_3) 4.83 (bs, 2H), 6.77 (dd, 1H), 6.86 (s, 1H), 6.97 (t, 1H), 7.31-7.24 (m, 1H), 7.57 (t, 1H), 7.81 (d, 1H), 8.02 (dd, 1H), 8.28 (d, 1H), 8.29 (s, 1H), 8.88 (s, 1H).

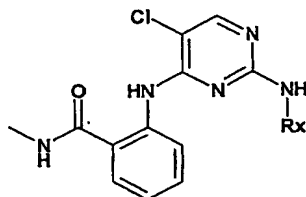
Preparation of 2-(5-bromo-2-chloropyrimidin-4-ylamino)benzenesulfonamide: To a solution of 5-bromo-2,4-dichloropyrimidine (300 mg, 1.32mmol) and 2-amino-benzenesulfonamide (340 mg, 1.97 mmol) in 2-propanol (3 mL), concentrated hydrochloric acid (0.06 mL) is added and the mixture is stirred at 90°C for 4.5 hours. The mixture is poured into aqueous sodium hydrogen carbonate and extracted with ethyl acetate three times. The organic layer is washed with water, dried over sodium sulfate, and evaporated in vacuo. The residue is purified by column chromatography (hexane : ethyl acetate = 2:1) to afford the title compound. R_f (hexane : ethyl acetate = 1:1): 0.55. ¹H-NMR (400MHz, CDCl₃) δ : 4.78 (br.s, 2H), 7.22 (dd, 1H), 7.61 (ddd, 1H), 7.95 (dd, 1H), 8.35 (s, 1H), 8.35 (d, 1H), 9.18 (s, 1H).

Example 7A: 2-[5-Chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide

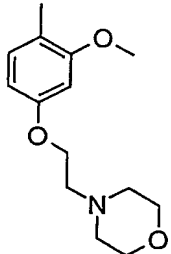
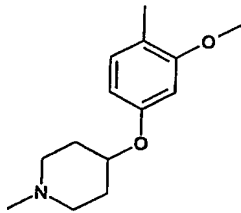
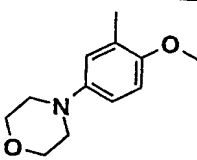
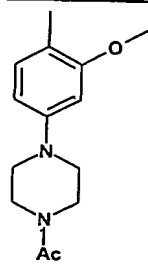
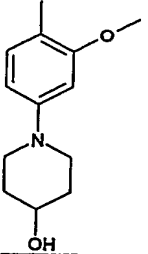


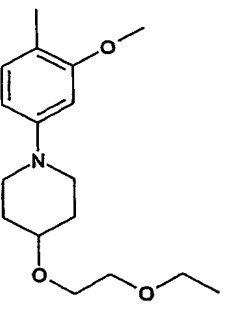
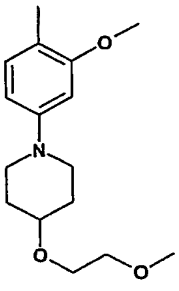
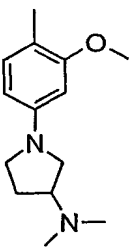
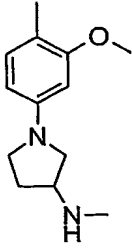
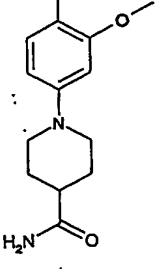
To a suspension of 2-(2,5-dichloro-pyrimidin-4-yl-amino)-N-methyl-benzamide (5.05 g, 17.0 mmol) in 90 mL of 2-methoxyethanol are added 2-methoxy-4-morpholinoaniline dihydrochloride (4.56 g, 16.2 mmol) and 17.0 mL of 1N ethanolic solution of hydrogen chloride (17.0 mmol). After the reaction mixture is stirred at 110°C for 4 hours and cooled to room temperature, the mixture is neutralized with 1N aqueous NaOH solution and extracted with EtOAc (100 mL × 3). The organic layer is washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The resulting black solid is washed with EtOH (90 mL), then purified with silica gel column chromatography (CH₂Cl₂ to CH₂Cl₂: AcOEt=1:2) to give 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide as a pale yellow solid. ¹H-NMR (400MHz, DMSO-d₆, δ): 2.80 (d, 3H, J = 4.52 Hz), 3.10-3.20 (m, 4H), 3.78 (s, 3H), 3.70-3.80 (m, 4H), 6.49 (dd, 1H, J = 8.56, 2.52 Hz), 6.66 (d, 1H, J = 2.52 Hz), 7.08 (dd, 1H, J = 8.04, 8.04 Hz), 7.44 (d, 1H, J = 8.56 Hz), 7.71 (dd, 1H, J = 8.04, 1.48 Hz), 8.10 (s, 1H), 8.13 (s, 1H), 8.59 (d, 1H, J = 8.04 Hz) 8.68-8.75 (m, 1H), 11.59 (s, 1H). MS m/z 469, 471 (M+1)⁺.

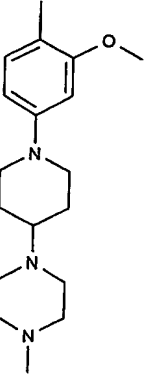
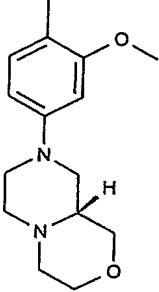
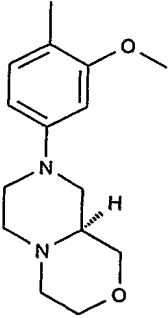
The following 2-[5-Chloro-2-(substituted phenylamino)-pyrimidin-4-ylamino]-N-methylbenzamide are prepared from 2-(2,5-Dichloro-pyrimidin-4-ylamino)-N-methyl-benzamide and the corresponding aniline following the procedure of Example 7A.



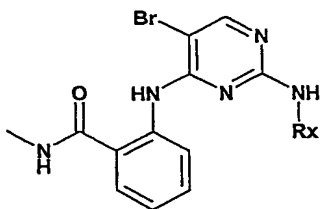
Exptl No.	Rx	Rf (solvent) or MS	NMR (400MHz) , δ (ppm)
7-1		MS: m/z 550, 552 (M+1)	DMSO-d ₆ : 1.44-1.33 (m, 2H), 1.64-1.45 (m, 6H), 1.73-1.89 (m, 2H), 2.34-2.44 (m, 1H), 2.43-2.55 (m, 4H), 2.65 (t, 2H), 2.80 (d, 3H), 3.75 (s, 3H), 3.72-3.75 (m, 2H), 6.48 (dd, 1H), 6.62 (d, 1H), 7.06 (t, 1H), 7.32 (t, 1H), 7.39 (d, 1H), 7.71 (dd, 1H), 8.09(s, 1H), 8.60 (d, 1H), 8.70 (d, 1H), 11.58 (s, 1H)
7-2		0.3 (MeOH: AcOEt =5:95)	CDCl ₃ : 1.70-1.97(m, 4H), 2.62-2.79(m, 1H), 3.04(d, 3H), 3.02-3.18(m, 2H), 3.23-3.33(m, 2H), 3.88 (s, 3H), 5.39-5.47(m, 1H), 6.15-6.24(m, 1H), 6.55-6.62(m, 2H), 6.74-6.82(m, 1H), 7.09 (dd, 1H), 7.23-7.32 (m, 1H), 7.46-7.52(m, 2H), 8.09(s, 1H), 8.15(d, 1H), 8.68(d, 1H) 11.0(bs, 1H)
7-3		MS (ESI) m/z 482, 484 (M+1) ⁺	DMSO-d ₆ : 2.24 (s, 3H), 2.45-2.55 (m, 4H), 2.80 (d, 3H, J = 4.52 Hz), 3.12-3.17 (m, 4H), 3.76 (s, 3H), 6.48 (dd, 1H, J = 8.56, 2.52 Hz), 6.63 (d, 1H, J = 2.52 Hz), 7.05-7.10 (m, 1H), 7.27-7.35 (m, 1H), 7.40 (d, 1H, J = 8.56 Hz), 7.69-7.72 (m, 1H), 8.09 (s, 1H), 8.12 (s, 1H), 8.55-8.65 (m, 1H), 8.67-8.75 (m, 1H), 11.59 (s, 1H)

7-4		0.46 (MeOH: CH ₂ Cl ₂ =1:4)	DMSO-d ₆ : 2.48-2.55(m, 4H), 2.71(t, 2H), 2.80(d, 3H), 3.58-3.61(m, 4H), 3.76(s, 3H), 4.11(t, 2H), 6.52(dd, 1H), 6.66(d, 1H), 7.06(dd, 1H), 7.32(dd, 1H), 7.46(d, 1H), 7.71(dd, 1H), 8.11(s, 1H), 8.19 (s, 1H), 8.54-8.60(m, 1H), 8.60-8.75(m, 1H), 11.6(s, 1H)
7-5		<i>m/z</i> 497, 499 (M+1) ⁺	DMSO-d ₆ : 1.60-1.70 (m, 2H), 1.90-1.98 (m, 2H), 2.13-2.25 (m, 2H), 2.19 (s, 3H), 2.60-2.67 (m, 2H), 2.80 (d, 3H, J = 4.52 Hz), 3.75 (s, 3H), 4.30-4.40 (m, 1H), 6.54 (dd, 1H, J = 8.56, 2.0 Hz), 6.65 (d, 1H, J = 2.0 Hz), 7.04-7.09 (m, 1H), 7.25-7.35 (m, 1H), 7.43 (d, 1H, J = 8.56 Hz), 7.68-7.73 (m, 1H), 8.10 (s, 1H), 8.18 (s, 1H) 8.52-8.59 (m, 1H), 8.68-8.75 (m, 1H), 11.57 (s, 1H)
7-6		0.25 (<i>n</i> -hexane: AcOEt=1:2)	CDCl ₃ : 2.95 (m, 4H), 3.03 (d, 3H), 3.75 (m, 4H), 3.86 (s, 3H), 6.21-6.19 (br, 1H), 6.49 (dd, 1H), 6.80 (d, 1H), 7.09-7.05 (m, 1H), 7.50 (dd, 1H), 8.08 (d, 1H), 8.13 (s, 1H), 8.68 (d, 1H), 11.07 (s, 1H)
7-7		MS <i>m/z</i> 510, 512 (M+1)	DMSO-d ₆ : 2.06 (s, 3H), 2.80 (d, 3H), 3.11 (t, 2H), 3.16 (t, 2H), 3.60 (dd, 4H), 3.77 (s, 3H), 6.51 (dd, 1H), 6.68 (d, 1H), 7.08 (dd, 1H), 7.33 (dd, 1H), 7.46 (d, 1H), 7.71 (d, 1H), 8.10(s, 1H), 8.12(s, 1H), 8.59-8.61 (bm, 1H), 8.70-8.71(bm, 1H), 11.59 (s, 1H)
7-8		0.48 (MeOH: AcOEt =5:95)	CDCl ₃ : 1.46(d, 1H), 1.68-1.82(m, 2H), 2.02-2.09(m, 2H), 2.83-2.96 (m, 2H), 3.03(d, 3H), 3.44-3.53(m, 2H), 3.82-3.92(m, 1H), 3.87(s, 3H), 6.15-6.23(m, 1H), 6.51 (d, 1H), 6.56(bs, 1H), 7.07(dd, 1H), 7.48(d, 2H), 8.08(s, 1H), 8.08-8.10(m, 1H), 8.69(d, 1H), 11.0(bs, 1H)

7-9		0.4 (<i>n</i> -hexane: AcOEt=1:1)	CDCl ₃ : 1.22 (t, 3H), 1.73-1.85 (m, 2H), 2.00-2.09 (m, 2H), 2.81-2.90 (m, 2H), 3.03 (d, 3H), 3.41-3.56 (m, 3H), 3.56 (dd, 2H), 3.58-3.62 (m, 2H), 3.64-3.68 (m, 2H), 3.86 (s, 3H), 6.15-6.24 (m, 1H), 6.50 (dd, 1H), 6.56 (d, 1H), 7.07 (dd, 1H), 7.24-7.30 (m, 1H), 7.45-7.52 (m, 2H), 8.08 (s, 1H), 8.06-8.08 (m, 1H), 8.69 (d, 1H), 11.0 (bs, 1H)
7-10		0.4 (<i>n</i> -hexane: AcOEt=1:1)	CDCl ₃ : 1.73-1.85 (m, 2H), 2.01-2.10 (m, 2H), 2.82-2.90 (m, 2H), 3.03 (d, 3H), 3.41 (s, 3H), 3.45-3.51 (m, 2H), 3.56-3.58 (m, 2H), 3.65-3.68 (m, 2H), 3.86 (s, 3H), 6.14-6.22 (m, 1H), 6.50 (dd, 1H), 6.56 (d, 1H), 7.07 (dd, 1H), 7.23-7.30 (m, 1H), 7.44-7.52 (m, 2H), 8.08 (s, 1H), 8.06-8.08 (m, 1H), 8.69 (d, 1H), 11.0 (bs, 1H)
7-11		0.54 (MeOH: CH ₂ Cl ₂ =1:4)	DMSO-d ₆ : 1.78-1.89 (m, 1H), 2.13-2.22 (m, 1H), 2.22 (s, 6H), 2.77-2.87 (m, 1H), 2.79 (d, 3H), 3.04-3.10 (m, 1H), 3.23-3.50 (m, 3H), 3.75 (s, 3H), 6.11 (dd, 1H), 6.22 (d, 1H), 7.05 (dd, 1H), 7.21-7.32 (m, 1H), 7.26 (d, 1H), 7.70 (d, 1H), 8.06 (s, 1H), 8.08 (s, 1H), 8.57-8.66 (m, 1H), 8.66-8.73 (m, 1H), 11.6 (s, 1H)
7-12		0.27 (MeOH: CH ₂ Cl ₂ =1:1)	DMSO-d ₆ : 1.77-1.87 (m, 1H), 2.09-2.18 (m, 1H), 2.35 (s, 3H), 2.79 (d, 1H), 3.02-3.07 (m, 1H), 3.23-3.50 (m, 4H), 3.74 (s, 3H), 6.09 (dd, 1H), 6.20 (d, 1H), 7.04 (dd, 1H), 7.22-7.32 (m, 1H), 7.26 (d, 1H), 7.70 (d, 1H), 8.05 (s, 1H), 8.08 (s, 1H), 8.57-8.67 (m, 1H), 8.67-8.73 (m, 1H), 11.6 (s, 1H)
7-13		0.23 (MeOH: AcOEt =5:95)	CDCl ₃ : 1.62-1.74 (m, 3H), 1.76-1.85 (m, 2H), 2.00-2.09 (m, 2H), 2.20-2.31 (m, 1H), 2.64-2.69 (m, 2H), 2.79 (d, 3H), 3.56-4.04 (m, 2H), 4.04 (s, 3H), 6.49 (dd, 1H), 6.63 (d, 1H), 6.78 (bs, 1H), 7.07 (dd, 1H), 7.28-7.38 (m, 1H), 7.39 (d, 1H), 7.71 (d, 1H), 8.09-8.11 (m, 2H), 8.09 (s, 1H), 8.60 (d, 1H), 8.71 (d, 1H), 11.6 (bs, 1H)

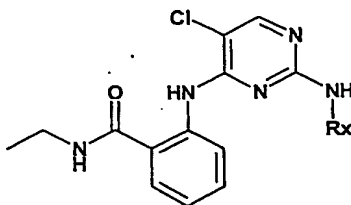
7-14		0.30 (MeOH: CH ₂ Cl ₂ =4:1)	DMSO-d ₆ : 1.61-1.46(m, 2H), 1.92-1.82 (m, 2H), 2.14 (s, 3H), 2.41-2.23 (m, 5H), 2.60-2.45 (m, 4H), 2.67 (t, 2H), 2.79 (d, 3H), 3.75 (s, 3H), 3.71-3.75 (m, 2H), 6.48 (dd, 1H), 6.63 (d, 1H), 7.10-7.03 (m, 1H), 7.34-7.27 (m, 1H), 7.43-7.35 (m, 1H), 7.71(dd, 1H), 8.09 (s, 1H), 8.11 (bs, 1H), 8.65-8.56 (bm, 1H), 8.75-8.67 (bm, 1H), 11.6 (s, 1H)
7-15		MS (ESI) <i>m/z</i> 524, 526 (M+1) ⁺	DMSO-d ₆ : 2.19-2.37 (m, 4H), 2.65-2.85 (m, 3H), 2.80 (d, 3H, J = 4.5 Hz), 3.15-3.21 (m, 1H), 3.48-3.59 (m, 2H), 3.61-3.67 (m, 1H), 3.72-3.81 (m, 1H), 3.76 (s, 3H), 6.47 (dd, 1H, J = 8.6, 2.5 Hz), 6.65 (d, 1H, J = 2.5 Hz), 7.04-7.10 (m, 1H), 7.28-7.35 (m, 1H), 7.42 (d, 1H, J = 8.6 Hz), 7.69-7.74 (m, 1H), 8.09 (s, 1H), 8.12 (s, 1H), 8.55-8.63 (m, 1H), 8.68-8.73 (m, 1H), 11.60 (s, 1H)
7-16		MS (ESI) <i>m/z</i> 524, 526 (M+1) ⁺	DMSO-d ₆ : 2.19-2.37 (m, 4H), 2.65-2.85 (m, 3H), 2.80 (d, 3H, J = 4.5 Hz), 3.15-3.21 (m, 1H), 3.48-3.59 (m, 2H), 3.61-3.67 (m, 1H), 3.72-3.81 (m, 1H), 3.76 (s, 3H), 6.47 (dd, 1H, J = 8.6, 2.5 Hz), 6.65 (d, 1H, J = 2.5 Hz), 7.04-7.10 (m, 1H), 7.28-7.35 (m, 1H), 7.42 (d, 1H, J = 8.6 Hz), 7.69-7.74 (m, 1H), 8.09 (s, 1H), 8.12 (s, 1H), 8.55-8.63 (m, 1H), 8.68-8.73 (m, 1H), 11.60 (s, 1H)

The following 2-[5-Bromo-2-(substituted phenylamino)-pyrimidin-4-ylamino]-N-ethyl-benzamide are prepared from 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-ethyl-benzamide and the corresponding aniline following the procedure of Example 7A

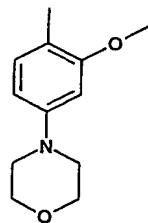
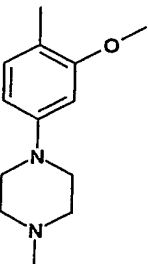
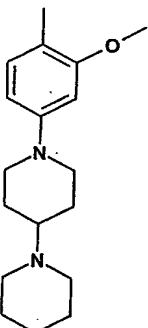
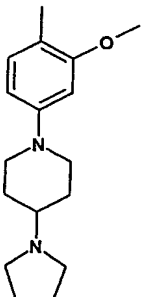


Expl No.	Rx	Rf (solvent) or MS	NMR
7-17		0.27 (<i>n</i> -hexane: AcOEt=1:2)	DMSO- <i>d</i> ₆ : 2.80(d, 3H), 2.88(t, 4H), 3.65 (m, 4H); 3.75 (s, 3H), 6.64 (dd, 1H), 6.94 (d, 1H), 7.11-7.08 (m, 1H), 7.38-7.34 (m, 1H), 7.47-7.46 (m, 1H), 7.70 (dd, 1H), 8.11 (s, 1H), 8.26 (s, 1H), 8.51-8.49 (m, 1H), 8.72-8.71 (m, 1H), 11.41 (s, 1H)
7-18		<i>m/z</i> 513, 515 (M+1)	DMSO- <i>d</i> ₆ : 2.79 (d, 3H, J = 4.04 Hz), 3.10-3.20 (m, 4H), 3.77 (s, 3H), 3.70-3.80 (m, 4H), 6.45-6.55 (m, 1H), 6.63-6.69 (m, 1H), 7.05-7.10 (m, 1H), 7.28-7.34 (m, 1H), 7.40-7.45 (m, 1H), 7.65-7.70 (m, 1H), 8.13 (s, 1H), 8.16 (s, 1H), 8.50-8.56 (m, 1H) 8.65-8.72 (m, 1H), 11.40 (s, 1H)
7-19		0.48 (<i>n</i> -Hexane: AcOEt=4:1)	DMSO- <i>d</i> ₆ : 2.80(d, 3H), 3.83(s, 3H), 4.11(t, 2H), 6.82(ddd, 1H), 7.03(dd, 1H), 7.15(dd, 1H), 7.44(dd, 1H), 7.73(d, 1H), 7.93(dd, 1H), 8.13(s, 1H), 8.33 (s, 1H), 8.50(d, 1H), 8.70-8.77(m, 1H), 11.3(s, 1H).

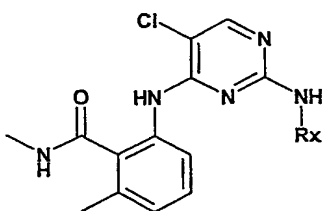
The following 2-[5-Chloro-2-(substituted phenylamino)-pyrimidin-4-ylamino]-N-ethyl-benzamide are prepared from 2-(2,5-Dichloro-pyrimidin-4-ylamino)-N-ethyl-benzamide and the corresponding aniline following the procedure of Example 7A



Expl No.	Rx	Rf (solvent) or MS	NMR (400MHz) , δ (ppm)
----------	----	--------------------	-------------------------------

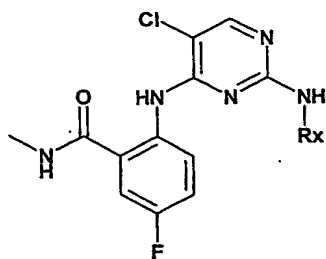
7-20		0.35 (n-hexane: AcOEt=1:2)	CDCl ₃ : 1.27 (t, 3H), 3.10-3.15 (m, 4H), 3.47-3.58 (m, 2H), 3.85-3.93 (m, 4H), 3.89 (s, 3H), 6.08-6.17 (m, 1H), 6.48 (dd, 1H), 6.53 (d, 1H), 7.05-7.11 (m, 1H), 7.42-7.53 (m, 2H), 8.08 (s, 1H), 8.12 (d, 1H), 8.67 (d, 1H), 10.94 (brs, 1H).
7-21		MS (ESI) <i>m/z</i> 497, 499 (M+1) ⁺	CDCl ₃ : 1.26 (t, 3H, J = 7.56Hz), 2.37 (s, 3H), 2.57-2.62 (m, 4H), 3.15-3.20 (m, 4H), 3.49 (dq, 2H, J = 7.56, 1.52 Hz), 3.87 (s, 3H), 6.11-6.16 (m, 1H), 6.49 (dd, 1H, J = 8.56, 2.52 Hz), 6.55 (d, 1H, J = 2.52 Hz), 7.05-7.10 (m, 1H), 7.23 (s, 1H), 7.41-7.50 (m, 2H), 8.07 (s, 1H), 8.08 (d, 1H, J = 8.56Hz), 8.65-8.69 (m, 1H), 10.93 (s, 1H)
7-22		<i>m/z</i> 564, 566 (M+1) ⁺	DMSO-d ₆ : 1.26 (t, 3H, J = 7.56Hz), 1.40-1.50 (m, 2H), 1.56-1.64 (m, 4H), 1.67-1.82 (m, 2H), 1.88-1.97 (m, 2H), 2.33-2.44 (m, 1H), 2.52-2.57 (m, 4H), 2.63-2.73 (m, 2H), 3.51 (dq, 2H, J = 7.56, 1.52 Hz), 3.62-3.69 (m, 2H), 3.86 (s, 3H), 6.10-6.15 (m, 1H), 6.49 (dd, 1H, J = 8.56, 2.52 Hz), 6.55 (d, 1H, J = 2.52 Hz), 7.05-7.10 (m, 1H), 7.23 (s, 1H), 7.43-7.50 (m, 2H), 8.05-8.11 (m, 1H), 8.07 (s, 1H), 8.65-8.69 (m, 1H), 10.91 (s, 1H)
7-23		0.39 (MeOH: CH ₂ Cl ₂ =1:4)	DMSO-d ₆ : 1.19 (t, 3H), 1.52-1.68 (m, 2H), 1.71-1.79 (m, 4H), 1.92-2.05 (m, 2H), 2.12-2.23 (m, 1H), 2.76-2.85 (m, 2H), 3.65-3.73 (m, 2H), 3.82 (s, 3H), 6.54 (dd, 1H), 6.69 (d, 1H), 7.13 (m, 1H), 7.45 (d, 1H), 7.79 (dd, 1H), 8.15 (s, 1H), 8.15-8.18 (m, 1H), 8.60-8.68 (m, 1H), 8.74-8.83 (m, 1H).

The following 2-[5-Chloro-2-(substituted phenylamino)-pyrimidin-4-ylamino]-6,N-dimethylbenzamide are prepared from 2-(2,5-Dichloro-pyrimidin-4-ylamino)-6,N-dimethyl-benzamide and the corresponding aniline following the procedure of Example 7A

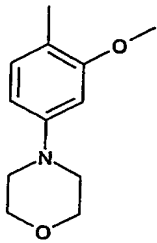
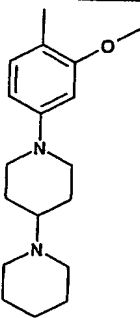


Exptl No.	Rx	Identification
7-24		NMR (400MHz, DMSO-d ₆ , δ): 1.58-1.68(m, 2H), 1.87-1.96(m, 2H), 2.13-2.22(m, 2H), 2.18(s, 3H), 2.18(s, 3H), 2.29(s, 3H), 2.57-2.65(m, 2H), 2.76(d, 3H), 3.75(s, 3H), 4.29-4.37(m, 1H), 6.45(dd, 1H), 6.61(d, 1H), 6.98(d, 1H), 7.18(dd, 1H), 7.47(d, 1H), 7.89(d, 1H), 8.02(s, 1H), 8.07 (s, 1H), 8.37-8.43(m, 1H), 8.49(s, 1H). Rf: 0.39 (MeOH: CH ₂ Cl ₂ =1:4).
7-25		NMR (400MHz, DMSO-d ₆ , δ): 1.35-1.42 (m, 2H), 1.45-1.60 (m, 6H), 1.75-1.85 (m, 2H), 2.29 (s, 3H), 2.30-2.35 (m, 1H), 2.43-2.50 (m, 4H), 2.57-2.66 (m, 2H), 2.76 (d, 3H, J = 5.0Hz), 3.65-3.74 (m, 2H), 3.76 (s, 3H), 6.40 (dd, 1H, J = 9.0, 2.0 Hz), 6.59 (d, 1H, J = 2.0 Hz), 6.98 (d, 1H, J = 7.6 Hz), 7.20 (dd, 1H, J = 7.6, 7.6 Hz), 7.43 (d, 1H, J = 9.0 Hz), 7.91-7.94 (m, 1H), 7.93 (s, 1H), 8.06 (s, 1H), 8.36-8.42 (m, 1H) 8.47 (s, 1H). MS (ESI) <i>m/z</i> 564, 566 (M+1) ⁺

The following 2-[5-Chloro-2-(substituted phenylamino)-pyrimidin-4-ylamino]-5-fluoro-N-methylbenzamide are prepared from 2-(2,5-Dichloro-pyrimidin-4-ylamino)-5-fluoro-N-methylbenzamide and the corresponding aniline following the procedure of Example 7A



Exptl No.	Rx	Identification
-----------	----	----------------

7-26		NMR (400MHz, DMSO-d ₆ , δ): 2.79 (d, 3H), 3.10-3.13 (m, 4H), 3.25-3.38 (m, 4H), 3.75 (s, 3H), 3.77-3.75 (m, 4H), 6.49 (dd, 1H), 6.65 (d, 1H), 7.30 (d, 1H), 7.84 (dd, 1H), 8.12(s, 1H), 8.40(s, 1H), 8.79-8.63 (bm, 1H), 8.76(d, 1H), 11.88 (s, 1H) MS (ESI): m/z 487, 489 (M+1).
7-27		NMR (400MHz, DMSO-d ₆ , δ): 1.68-1.33 (m, 8H), 1.93-1.73 (m, 2H), 2.35-2.60 (m, 1H), 2.62-2.74 (m, 2H), 2.67 (t, 2H), 2.74 (d, 3H), 3.25-3.38 (m, 4H), 3.76 (s, 3H), 3.83-3.71 (m, 2H), 6.48 (dd, 1H), 6.49 (dd, 1H), 6.63 (d, 1H), 7.15 (dd, 1H), 7.36 (d, 1H), 7.57 (dd, 1H), 8.09(s, 1H), 8.12(s, 1H), 8.65-8.55 (bm, 1H), 8.78(d, 1H), 11.39 (s, 1H) MS (ESI): m/z 568, 570 (M+1)

Preparation of 7-[5-Chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-2-methyl-2,3-dihydro-isoindol-1-one (TAE836 7-28)

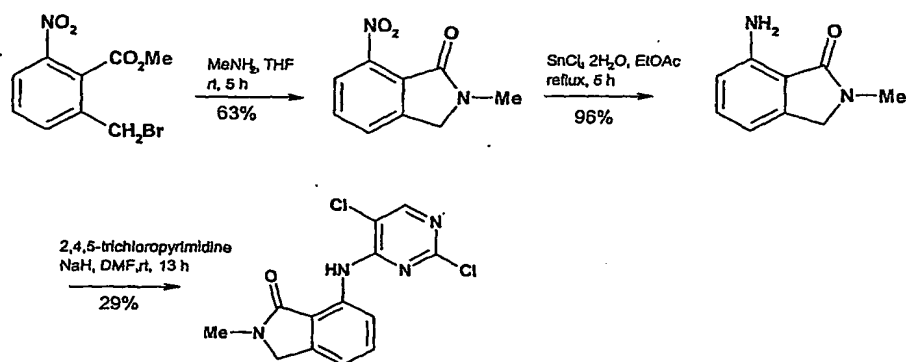
Synthetic procedure for 7-(2,5-Dichloro-pyrimidin-4-ylamino)-2-methyl-2,3-dihydro-isoindol-1-one

N-Methyl-7-nirto-2,3-dihydroisoindole-1-one. At room temperature, a solution of methyl 2-bromomethyl-6-nitrobenzoate (1.26 g, 4.63 mmol) in THF (13 mL) is treated with 2M soln. of methylamine in THF (14 mL), stirred for 5 h, diluted with EtOAc (100 mL), washed with sat. aqueous solution of NaHCO₃ (15 mL) and brine (15 mL), dried (MgSO₄), and evaporated. A flash chromatography (30 g of silica gel; CH₂Cl₂/EtOAc 1:1) gives *N-Methyl-7-nirto-2,3-dihydroisoindole-1-one* (0.561 g, 2.92 mmol) in 63%. Yellow solid. *R_f* (CH₂Cl₂/EtOAc 1:1) 0.46. ¹H-NMR (400 MHz, CDCl₃) 3.21 (s), 4.44 (s), 7.63 – 7.69 (m, 2 H), 7.70 – 7.75 (m, 1 H).

7-Amino-N-methyl-2,3-dihydroisoindole-1-one. At room temperature, a solution of *N-Methyl-7-nirto-2,3-dihydroisoindole-1-one* (561.0 mg, 2.92 mmol) in EtOAc (8.4 mL) is treated with SnCl₂·2H₂O (2.68 g), stirred at 80°C under reflux for 5 h, and treated with 30 mL of 5N NaOH at 0°C. After the both layers are separated, the aqueous layer is extracted with EtOAc (2 x 8 mL), the combined extracts are washed with brine (5 mL), dried (MgSO₄), and evaporated to give *7-Amino-N-methyl-2,3-dihydroisoindole-1-one* (455.9 g, 2.81 mmol) in 96%. Yellow solid.

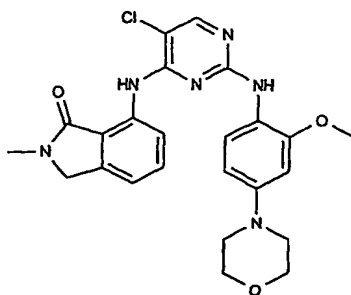
R_f (CH₂Cl₂/EtOAc 1:1) 0.53. ¹H-NMR (400 MHz, CDCl₃) 3.12 (s), 4.28 (s), 5.20 (br. s), 6.56 (d, $J = 8.0$), 6.68 (d, $J = 8.0$), 7.21 (t, $J = 8.0$).

7-(4-Amino-2,5-dichloropyrimidin-4-yl)amino-N-methyl-2,3-dihydroisoindole-1-one. At 0°C, a solution of 7-Amino-N-methyl-2,3-dihydroisoindole-1-one (232.6 mg, 1.43 mmol) in DMF (2.0 mL) is treated with 60% NaH (89.8 mg), stirred at the same temperature for 1.5 h, treated with a solution of 2,4,5-trichloropyrimidine (0.557 g) in DMF (3.5 mL), stirred for 1 h, and warmed to room temperature. After furthermore stirring for 13 h, the mixture is treated with sat. aqueous NH₄Cl (6 mL), and the resulting brown precipitates are collected by a filtration, followed by washing with H₂O, hexane, and CH₃CN to give 7-(4-Amino-2,5-dichloropyrimidin-4-yl)amino-N-methyl-2,3-dihydroisoindole-1-one (130.2 g, 0.416 mmol) in 26%. Brown solid. R_f (CH₂Cl₂/EtOAc 1:1) 0.50. ¹H-NMR (400 MHz, CDCl₃): 3.22 (s), 4.43 (s), 7.15 (d, $J = 8.0$), 7.59 (t, $J = 8.0$), 8.24 (s), 8.71 (d, $J = 8.0$), 11.05 (br. s).



The following 7-[5-Chloro-2-(substituted phenylamino)-pyrimidin-4-ylamino]-2-methyl-2,3-dihydro-isoindol-1-one are prepared from 7-(2,5-Dichloro-pyrimidin-4-ylamino)-2-methyl-2,3-dihydro-isoindol-1-one and the corresponding aniline following the procedure of Example 7A.

7-[5-Chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-2-methyl-2,3-dihydro-isoindol-1-one (TAE836 7-29)



¹H-NMR (400MHz, DMSO-d₆, δ): 3.07 (s, 3H), 3.13-3.17 (m, 4H), 3.75 (s, 3H), 3.34-3.78 (m, 4H), 4.46 (s, 2H), 6.54 (dd, 1H, J = 8.6, 2.5 Hz), 6.67 (d, 1H, J = 2.5 Hz), 7.15 (d, 1H, J = 7.6 Hz), 7.25-7.34 (m, 1H) 7.36 (d, 1H, J = 8.6 Hz), 8.13 (s, 1H), 8.36 (s, 1H), 8.37-8.50 (m, 1H) 10.57 (s, 1H). MS (ESI) *m/z* 481. 483 (M+1)⁺

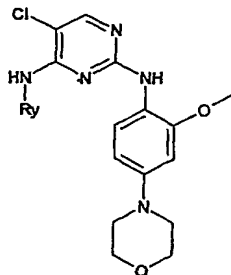
Example 7B: 2-[5-Chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide (alternative synthesis to Example 7A)

To a suspension of 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-benzoic acid (5.5 g, 12.1 mmol) in 100 mL of THF are added Et₃N (2.06 mL, 14.8 mmol) and isobutyl chloroformate (1.7 mL, 12.8 mmol) at -5°C. After stirring at the same temperature for 30 min, the reaction mixture is further stirred at room temperature for 1 hour and then H₂O is added to the reaction mixture. The resulting precipitate is collected by filtration, washed with H₂O, and dried under reduced pressure to give an intermediate (4.80 g) (10.96 mmol, 91%) as yellow solid.

NMR (400MHz, DMSO-d₆, δ): 3.10-3.20 (m, 4H), 3.70-3.80 (m, 4H), 3.93 (s, 3H), 6.53 (dd, 1H, J = 9.08, 2.0 Hz), 6.70 (d, 1H, J = 2.0 Hz), 7.49-7.54 (m, 1H), 7.67 (d, 1H, J = 8.56 Hz), 7.89 (s, 1H), 7.85-7.95 (m, 1H), 8.23 (d, 1H, J = 9.08 Hz), 8.26 (d, 1H, J = 8.56Hz), 12.60 (s, 1H).

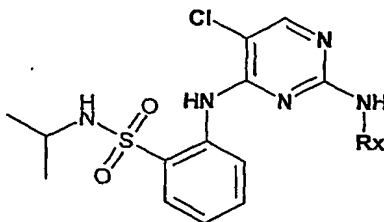
To a 1M solution of methylamine in THF (560 μl, 0.56 mmol) is added 82 mg of the obtained intermediate (0.187 mmol) followed by 1M solution of NaHMDS in THF (560 μl, 0.56 mmol) dropwise. After the reaction mixture is stirred for 10 minutes, 5 mL of H₂O is added and extraction is performed with AcOEt. The organic layer is washed with brine, dried over Na₂SO₄, concentrated under reduced pressure, and purified by silica gel column chromatography (Hexane: AcOEt=1:1 to AcOEt) to give the title compound as a pale yellow solid. Data are given in Example 7A.

By repeating the procedures described above using appropriate starting materials and conditions the following compounds are obtained as identified below.

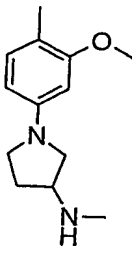
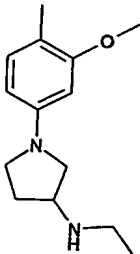
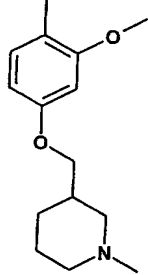
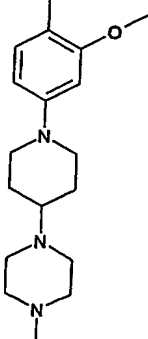
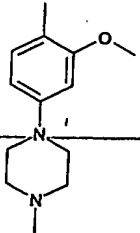


Exptl No.	Ry	Rf (solvent) or MS	NMR (400MHz), δ (ppm)
7-30		0.10 (n-hexane: AcOEt=1:1)	CDCl ₃ : 3.02-3.19 (m, 10H), 3.83-3.91 (m, 4H), 3.87 (s, 3H), 6.45 (dd, 1H), 6.52 (d, 1H), 7.09-7.14 (m, 1H), 7.29 (m, 1H), 7.31 (dd, 1H), 7.38-7.45 (m, 1H), 8.06 (s, 1H), 8.14 (d, 1H), 8.39 (d, 1H), 8.97 (s, 1H).
7-31		0.36 (n-hexane: AcOEt=1:2)	CDCl ₃ : 1.27 (d, 6H), 3.09-3.16 (m, 4H), 3.81-3.92 (m, 4H), 3.89 (s, 3H), 4.26-4.37 (m, 1H), 5.93-5.98 (m, 1H), 6.48 (dd, 1H), 6.53 (d, 1H), 7.05-7.11 (m, 1H), 7.42-7.49 (m, 2H), 8.08 (s, 1H), 8.12 (d, 1H), 8.65 (d, 1H), 10.88 (br.s, 1H).

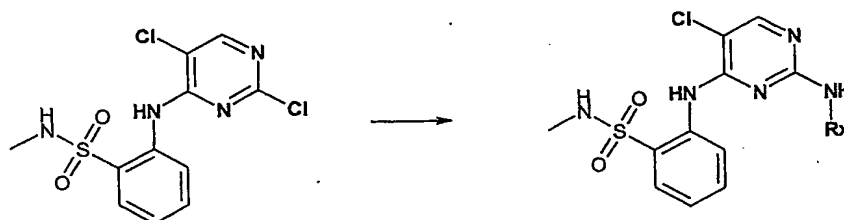
The following 2-[5-chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino]-N-isopropyl-benzene-sulfonamides are prepared from 2-(5-chloro-2-chloro-pyrimidin-4-ylamino)-N-isopropyl-benzenesulfonamide and the corresponding aniline following the procedure of Example 7A



Exptl No.	Rx	Rf (solvent) Or MS	NMR (400MHz), δ (ppm)
-----------	----	--------------------	------------------------------

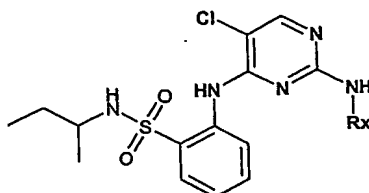
7-32		0.39 (MeOH: CH ₂ Cl ₂ =1:4)	DMSO-d ₆ : 0.94(d, 6H), 1.75-1.84(m, 1H), 2.07-2.16(m, 1H), 2.33(s, 3H), 2.98-3.04(m, 1H), 3.22-3.36(m, 5H), 3.42-3.47(m, 1H), 3.74(s, 3H), 6.05(dd, 1H), 6.18(d, 1H), 7.18(dd, 1H), 7.25(d, 1H), 7.35-7.45(m, 1H), 7.77-7.82(m, 1H), 7.70-8.10(m, 1H), 8.09-8.17 (m, 2H), 8.45-8.63(m, 1H), 9.34(s, 1H)
7-33		0.40 (<i>n</i> -hexane: AcOEt=1:1)	CDCl ₃ : 1.00(d, 6H), 1.13(t, 3H), 1.83-1.92(m, 1H), 2.23-2.30(m, 1H), 2.70-2.78(m, 2H), 3.08-3.13(m, 1H), 3.27-3.54 (m, 5H), 3.85(s, 3H), 4.33(d, 1H), 6.05(d, 1H), 6.13(s, 1H), 7.13(bs, 1H), 7.18-7.22(m, 1H), 7.52-7.56(m, 1H), 7.83-7.86(m, 1H), 7.95-7.98(m, 1H), 8.09(s, 1H), 8.47-8.49(m, 1H), 8.89(s, 1H)
TAE 626 7-34		0.30 (<i>n</i> -hexane: AcOEt=1:1)	CDCl ₃ : 0.93 (d, 6H), 1.05-1.09(m, 1H), 1.48-1.99(m, 6H), 2.16(s, 3H), 2.61-2.67(m, 1H), 2.80-2.83(m, 1H), 3.75(s, 3H), 3.80-3.89(m, 2H), 6.44-6.47(m, 1H), 6.62-6.63(m, 1H), 7.18-7.22(m, 1H), 7.42-7.46(m, 1H), 7.80-7.89(m, 2H), 8.17(s, 1H), 8.23(s, 1H), 8.42-8.44(m, 1H), 8.89(s, 1H)
7-35		0.69 (MeOH: CH ₂ Cl ₂ =1:3)	DMSO-d ₆ : 0.94(d, 6H), 1.45-1.57(m, 2H), 1.80-1.88(m, 2H), 2.14(s, 3H), 2.25-2.35(m, 4H), 2.45-2.55(m, 4H), 2.62-2.70(m, 2H), 3.28-3.37(m, 1H), 3.68-3.74(m, 2H), 3.75(s, 3H), 6.44(dd, 1H, <i>J</i> =8.82, 2.0Hz), 6.61(d, 1H, <i>J</i> =2.0Hz), 7.21(dd, 1H), 7.37(d, 1H), 7.45(dd, 1H), 7.81(dd, 1H, <i>J</i> =1.82, 1.52Hz), 7.84-7.92(m, 1H), 8.12-8.20(m, 1H), 8.16(s, 1H), 8.43 - 8.51(m, 1H), 9.31(s, 1H)
7-36		0.35 (<i>n</i> -hexane: AcOEt=1:1)	CDCl ₃ : 0.93(d, 6H), 2.23(s, 3H), 2.45-2.48(m, 4H), 3.12-3.15(m, 4H), 3.75(s, 3H), 6.42-6.45(m, 1H), 6.63 (s, 1H), 7.19-7.23(m, 1H), 7.38-7.47(m, 2H), 7.80-7.89(m, 2H), 8.16(s, 1H), 8.46-8.48(m, 1H), 9.34(s, 1H)

The following 2-[5-chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzene-sulfonamides are prepared from 2-(5-chloro-2-chloro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide and the corresponding aniline following the procedure of Example A

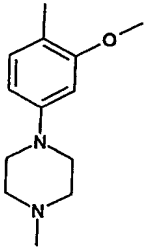


Exptl No.	Rx	R _f (solvent) or MS	NMR (400MHz), δ (ppm)
7-37		0.50 (AcOEt)	CDCl ₃ : 2.63(d, 3H), 3.14(t, 4H), 3.87-3.90(m, 7H), 4.64(bm, 1H), 6.45(dd, 1H), 6.55(d, 1H), 7.23-7.26(m, 1H), 7.51-7.55(m, 1H), 7.91(d, 1H), 7.95(dd, 1H), 8.06(s, 1H), 8.47(d, 1H), 9.26(s, 1H)
7-38		m/z 546, 548 (M+1)	DMSO-d ₆ : 2.06 (s, 3H), 2.43 (s, 3H), 3.10 (m, 2H), 3.16 (m, 2H), 3.59-3.62 (m, 4H), 3.77 (s, 3H), 6.49 (dd, 1H), 6.68 (d, 1H), 7.21-7.25 (m, 1H), 7.42 (d, 1H), 7.49 (dd, 1H), 7.75-7.77 (m, 1H), 7.78(s, 1H), 8.16(s, 1H), 8.21 (s, 1H), 8.50(d, 1H), 9.35 (s, 1H)

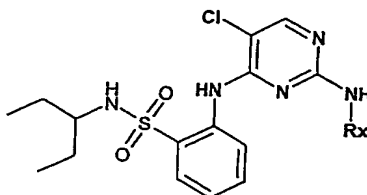
The following 2-[5-chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino]-N-sec-butyl-benzene-sulfonamides are prepared from 2-(5-chloro-2-chloro-pyrimidin-4-ylamino)-N-sec-butyl-benzenesulfonamide and the corresponding aniline following the procedure of Example 7A

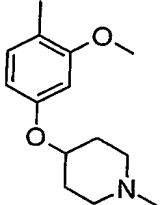
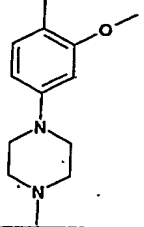


Exptl No.	Rx	R _f (solvent) or MS	NMR (400MHz) , δ (ppm)
-----------	----	--------------------------------	-------------------------------

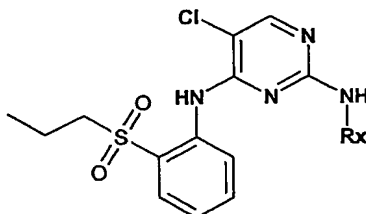
7-39		0.35 (<i>n</i> -hexane: AcOEt=1:1)	CDCl ₃ : 0.62(t, 3H), 0.88(d, 3H), 1.22-1.29(m, 2H), 2.23(s, 3H), 2.45-2.47(m, 4H), 3.05-3.14(m, 5H), 3.75(s, 3H), 6.40-6.43(m, 1H), 6.62(s, 1H), 7.18-7.22(m, 1H), 7.39-7.47(m, 2H), 7.80-7.82(m, 1H), 8.15-8.16(m, 2H), 8.44-8.46(m, 1H), 9.32(s, 1H)
------	---	---	--

The following 2-[5-chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino]-N-(1-ethyl-propyl)-benzenesulfonamides are prepared from 2-(5-chloro-2-chloro-pyrimidin-4-ylamino)-N-(1-ethyl-propyl)-benzenesulfonamide and the corresponding aniline following the procedure of Example 7A

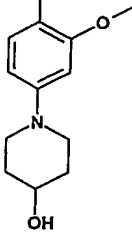
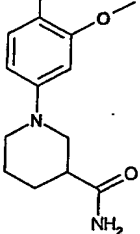


Exptl No.	Rx	R _f (solvent) or MS	NMR (400MHz), δ (ppm)
7-40		0.46 (MeOH: CH ₂ Cl ₂ =3:7)	DMSO-d ₆ : 0.58(t, 6H), 1.14-1.34(m, 4H), 1.58-1.68(m, 2H), 1.87-1.96(m, 2H), 2.12-2.22(m, 2H), 2.18(s, 3H), 2.57-2.65(m, 2H), 2.86-2.96(m, 1H), 3.75(s, 3H), 4.30-4.39(m, 1H), 6.46(dd, 1H), 6.63(d, 1H), 7.19(t, 1H), 7.39-7.48(m, 2H), 7.75-7.84(m, 2H), 8.18(s, 1H), 8.20(s, 1H), 8.39(m, 1H), 9.33(bs, 1H)
7-41		0.35 (<i>n</i> -hexane: AcOEt=1:1)	CDCl ₃ : 0.59(t, 6H), 1.14-1.34(m, 4H), 2.23(s, 3H), 2.45-2.47(m, 4H), 2.90-2.95(m, 1H), 3.11-3.14(m, 4H), 3.76(s, 3H), 6.39-6.42(m, 1H), 6.62(s, 1H), 7.18-7.22(m, 1H), 7.41-7.46(m, 2H), 7.76-7.82(m, 2H), 8.12(s, 1H), 8.16(s, 1H), 8.43-8.44(m, 1H), 9.35(s, 1H)

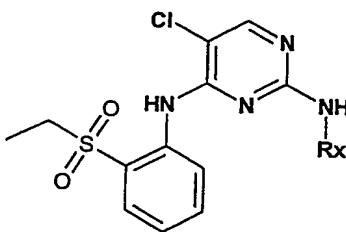
The following 5-Chloro-N²-(substituted phenyl)-N⁴-[2-(propane-1-sulfonyl)-phenyl]-pyrimidine-2,4-diamine are prepared from (2,5-Dichloro-pyrimidin-4-yl)-[2-(propane-1-sulfonyl)-phenyl]-amine and the corresponding aniline following the procedure of Example 7A

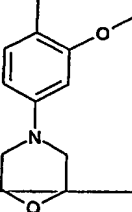


Exptl No.	Rx	R _f (solvent) or MS	NMR (400MHz) , δ (ppm)
7-42		0.58 (AcOEt)	CDCl ₃ : 0.97(t,3H), 1.72-1.82(m, 2H), 3.08-3.14(m, 6H), 3.87-3.89(m, 7H), 6.46(dd, 1H), 6.53(d,1H), 7.24-7.28(m,1H), 7.30(s, 1H), 7.60-7.64(m, 1H), 7.94(dd, 1H), 8.05(d, 1H), 8.15(s, 1H), 8.59(d, 1H), 9.40(s, 1H)
7-43		0.57 (MeOH: AcOEt=1:4)	CDCl ₃ : 0.98(t, 3H), 1.85-1.68(m, 2H), 2.15(s, 3H), 3.16-3.07(m, 6H), 3.67-3.62(m, 2H), 3.81-3.78(m, 2H), 3.89(s, 3H), 6.47(d, 1H), 6.55(d, 1H), 7.36-7.33(m, 1H), 7.62 (t, 1H), 7.95(dd, 1H), 8.08(d, 1H), 8.15(s, 1H), 8.58(d, 1H), 9.41(s, 1H)
7-44		0.13 (MeOH: AcOEt=1:4)	CDCl ₃ : 0.97(t, 3H), 1.43-1.52(m, 2H), 1.52-1.67 (m, 4H), 1.69-1.72(m, 4H), 1.90-1.98(m, 2H), 2.34-2.46(m, 1H), 2.51-2.59(m, 4H), 2.64-2.74(m, 2H), 3.11(dd, 2H), 3.64-3.73(m, 2H), 3.87(s, 3H), 6.47(dd, 1H), 6.56 (d, 1H), 7.24-7.33(m, 1H), 7.62(t, 1H), 7.94(dd, 1H), 8.00(d, 1H), 8.14(s, 1H), 8.59(d, 1H), 9.39(bs, 1H).

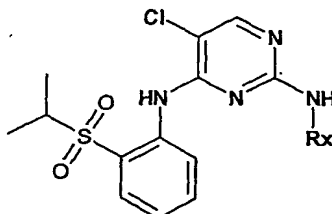
7-45		0.22 (AcOEt)	CDCl ₃ : 0.97(t, 3H), 1.45(d, 1H), 1.68-1.82(m, 4H), 2.0-2.1(m, 2H), 2.91(dt, 2H), 3.10(dt, 2H), 3.46-3.51 (m, 2H), 3.84-3.92(m, 1H), 3.88 (s, 1H), 6.48(dd, 1H), 6.57(d, 1H), 7.23-7.32 (m, 1H), 7.62(dd, 1H), 7.94(dd, 1H), 8.02 (dd, 1H), 8.14(s, 1H), 8.59(d, 1H), 9.39(bs, 1H)
7-46		0.1 (AcOEt)	CDCl ₃ : 0.97(t, 3H), 1.71-1.82(m, 2H), 1.86-1.98(m, 2H), 2.01-2.08(m, 2H), 2.25-2.37(m, 2H), 2.75 (dt, 2H), 3.10(dt, 1H), 3.63-3.66(m, 2H), 3.88(s, 3H), 5.25-5.40(bm, 1H), 5.40-5.58 (bm, 1H), 6.48(dd, 1H), 6.57(d, 1H), 7.22-7.34 (m, 1H), 7.62(ddd, 1H), 7.93 (d, 1H), 7.94 (dd, 1H), 8.14(s, 1H), 8.59(d, 1H), 9.40(bm, 1H)

The following 5-Chloro-N²-(substituted phenyl)-N⁴-[2-ethanesulfonyl-phenyl]-pyrimidine-2,4-diamine are prepared from (2,5-Dichloro-pyrimidin-4-yl)-[2-ethanesulfonyl-phenyl]-amine and the corresponding aniline following the procedure of Example 7A

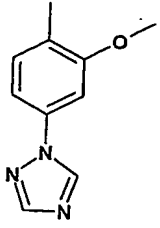
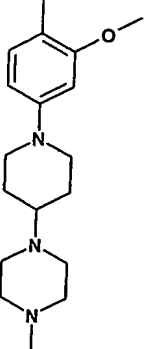


Exptl No.	Rx	R _f (solvent) or MS	NMR (400MHz) , δ (ppm)
7-47		0.53 (AcOEt)	CDCl ₃ : 1.28(t, 3H), 3.12-3.19(m, 6H), 3.87-3.89(m, 7H), 6.45(dd, 1H), 6.53(d, 1H), 7.24-7.28(m, 1H), 7.31(s, 1H), 7.60-7.64(m, 1H), 7.95(dd, 1H), 8.04(d, 1H), 8.14(s, 1H), 8.58(d, 1H), 9.39(s, 1H)

The following 5-Chloro-N²-(substituted phenyl)-N⁴-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine are prepared from (2,5-Dichloro-pyrimidin-4-yl)-[2-(propane-2-sulfonyl)-phenyl]-amine and the corresponding aniline following the procedure of Example 7A



Exptl No.	Rx	Rf (solvent) or MS	NMR (400MHz) , δ (ppm)
7-48		0.2 (AcOEt)	CDCl ₃ : 1.24(d, 6H) ,1.98-1.90(m, 2H), 2.07-1.99(m, 2H), 2.35-2.28(m, 1H), 2.80-2.71 (m, 2H), 3.28-3.21(m, 1H), 3.68-3.63(m, 2H), 3.88(s, 3H), 5.35-5.26(bm, 1H), 5.54-5.43 (bm, 1H), 6.49(d, 1H), 6.56(d, 1H), 7.34-7.28 (m, 1H), 7.62(dd, 1H), 7.91 (dd, 1H), 8.03 (d, 1H), 8.13(s, 1H), 8.60(d, 1H), 9.54(bm, 1H)
7-49		MS m/z 561, 563 (M+1).	CDCl ₃ : 1.31(d, 6H), 2.64 (t, 2H), 2.68-2.77 (m, 4H), 3.19(t, 4H), 3.17-3.28(m, 1H), 3.68(t, 2H), 3.88(s, 3H), 6.48(dd, 1H), 6.55 (d, 1H), 7.23-7.32(m, 1H), 7.62(ddd, 1H), 7.91(dd, 1H), 8.04(dd, 1H), 8.12(s, 1H), 8.60(d, 1H), 9.54(bs, 1H)
7-50		0.55 (AcOEt)	CDCl ₃ : 1.31(d, 6H), 3.12-3.14(m, 4H), 3.21-3.27(m, 1H), 3.87-3.89(m, 7H), 6.46(dd, 1H), 6.53(d, 1H), 7.23-7.27(m, 1H), 7.30(s, 1H), 7.59-7.64(m, 1H), 7.91(dd, 1H), 8.05(d, 1H), 8.14(s, 1H), 8.60(d, 1H), 9.55(s, 1H)

7-51		0.37 (AcOEt)	CDCl ₃ : 1.32(d, 6H), 3.21-3.27(m, 1H), 4.00(s, 1H), 7.11(dd, 1H), 7.26-7.27(m, 1H), 7.29-7.33(m, 1H), 7.64(s, 1H), 7.66-7.71(m, 1H), 7.95(dd, 1H), 8.10(s, 1H), 8.21(s, 1H), 8.46(d, 1H), 8.50(s, 1H), 8.54(d, 1H), 9.59(s, 1H)
7-52		0.03 (AcOEt)	CDCl ₃ : 1.31(d, 6H), 1.67-1.77(m, 2H), 1.95-2.05 (m, 2H), 2.39-2.48 (m, 1H), 2.48-2.61(m, 2H), 2.63-2.78(m, 8H), 3.24 (ddd, 1H), 3.71-3.63 (m, 2H), 3.87(s, 3H), 6.47(dd, 1H), 6.55 (d, 1H), 7.21-7.28(m, 1H), 7.61(ddd, 1H), 7.91(dd, 1H), 8.00(d, 1H), 8.12(s, 1H), 8.60(d, 1H), 9.53(bs, 1H)

Example 8: Synthesis of substituted amines which are commercially not available:

Preparation of 3-amino-4'-methoxy-4-methylbiphenyl

To a solution of 4-methoxyphenyl-boronic acid (500 mg, 3.29 mmol) in toluene (5.2 mL) and ethanol (1.3 mL), potassium carbonate (910 mg, 6.58 mmol), tetrakis(triphenylphosphine)-palladium (228.1 mg, 0.099 mmol) and 4-bromo-1-methyl-2-nitrobenzene (711 mg, 3.29 mmol) are added and stirred at 100°C for 7 hours. The mixture is poured into water and extracted with ethyl acetate two times. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1) to afford the 4'-methoxy-4-methyl-3-nitrobiphenyl as a yellow solid.

¹H-NMR (δ, ppm) : 2.62 (s, 3H), 3.86 (s, 3H), 7.02-6.98 (m, 2H), 7.37 (d, 1H), 7.54 (dd, 2H), 7.68 (dd, 1H), 8.18 (d, 1H). R_f (hexane : ethyl acetate = 3:1): 0.40.

A suspension of 4'-methoxy-4-methyl-3-nitrobiphenyl (630 mg, 2.95 mmol) and 10% palladium on charcoal (63 mg, 0.059 mmol) in methanol (6 mL) is stirred under hydrogen atmosphere for 12 hours. ~~Palladium catalyst is removed by filtration and the resulting solution is evaporated in~~
vacuo to afford the title compound.

¹H-NMR (δ, ppm) : 2.20 (s, 3H), 3.84 (s, 3H), 6.87 (d, 1H), 6.89 (dd, 1H), 6.95 (d, 2H), 7.09 (d, 1H), 7.48 (d, 2H). R_f (n-hexane : ethyl acetate = 1:1): 0.50.

Preparation of 4-(3-amino-4-methylbenzoyl)-piperazine-1-carboxylic acid tert-butyl ester

To a solution of 4-methyl-3-nitro-benzoic acid (300 mg, 2.76 mmol), N-butoxycarbonyl-piperazine (340 mg, 1.83 mmol) in DMF (3.0 mL), triethylamine (300 μ L, 3.59 mmol), TBTU (800 mg, 2.49 mmol) and HOAt (270.5 mg, 1.99 mmol) are added and stirred at room temperature for 24 hours. The mixture is poured into water and extracted twice with ethyl acetate. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1) to afford 4-(4-methyl-3-nitrobenzoyl)-piperazine-1-carboxylic acid tert-butyl ester as a colorless solid.

$^1\text{H-NMR}$ (δ , ppm) : 1.47 (s, 9H), 2.64 (s, 3H), 3.28-3.88 (bm, 8H), 7.42 (d, 1H), 7.56 (dd, 1H), 8.03 (d, 1H). Rf (hexane : ethyl acetate = 10:1): 0.13.

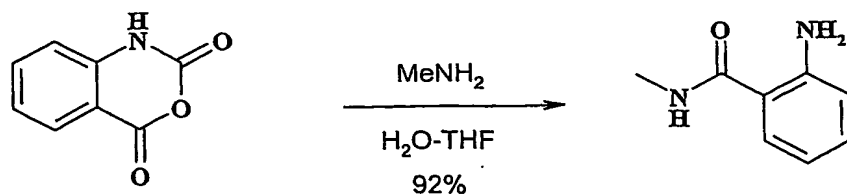
The title compound is obtained by reduction with hydrogen over 10% palladium on charcoal in methanol solution.

Preparation of 4-(3-amino-4-methylphenyl)-morpholine

To a solution of 4-bromo-1-methyl-2-nitrobenzene (225 mg, 1.04 mmol), morpholine (125 μ L, 1.25 mmol), and cesium carbonate (474.4 mg, 1.46 mmol) in toluene, palladium diacetate (31.2 mg, 0.139 mmol) and 2-(di-*t*-butylphosphino)biphenyl (125 mg, 0.403 mmol) are added and stirred at 100°C for 5 hours. After cooling, the mixture is filtered to remove insoluble material. The filtrate is poured into water and extracted with ethyl acetate twice. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1) to afford 4-(4-methyl-3-nitrophenyl)-morpholine as a yellow solid.

$^1\text{H-NMR}$ (δ , ppm) : 2.50 (s, 3H), 3.17-3.19 (m, 4H), 3.86-3.88 (m, 4H), 7.04 (dd, 1H), 7.21 (d, 1H), 7.47 (d, 1H). Rf (hexane : ethyl acetate = 5:1): 0.20.

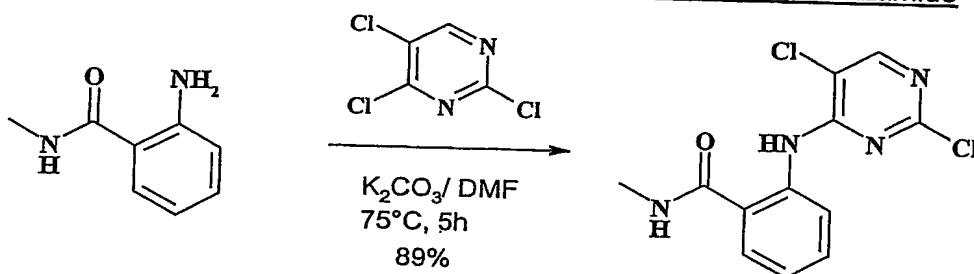
The title compound is obtained by reduction with hydrogen over 10% palladium on charcoal in methanol solution.

Preparation of 2-amino-N-methyl-benzamide

To a suspension of 16.3 g (100 mmol) of isatoic anhydride in 100 mL of H₂O is added portionwise 100 mL of 2N methylamine - tetrahydrofuran solution (200 mmol) at room temperature. The reaction mixture is stirred for 1 hour and then extracted with AcOEt. The organic layer is washed with H₂O and brine, dried over Na₂SO₄, and concentrated under reduced pressure to give 13.79 g of the desired product, 2-amino-*N*-methyl-benzamide (92 mmol, 92%) as colorless solid.

NMR (400MHz, CDCl₃, δ): 2.97 (d, 3H, J = 4.52 Hz), 5.49 (bs, 1H), 6.07 (bs, 1H), 6.64 (ddd, 1H, J = 8.04, 7.56, 1.0 Hz), 6.68 (dd, 1H, J = 8.32, 1.0 Hz), 7.20 (ddd, 1H, J = 8.32, 7.56, 1.52 Hz), 7.29 (dd, 1H, J = 8.04, 1.52 Hz).

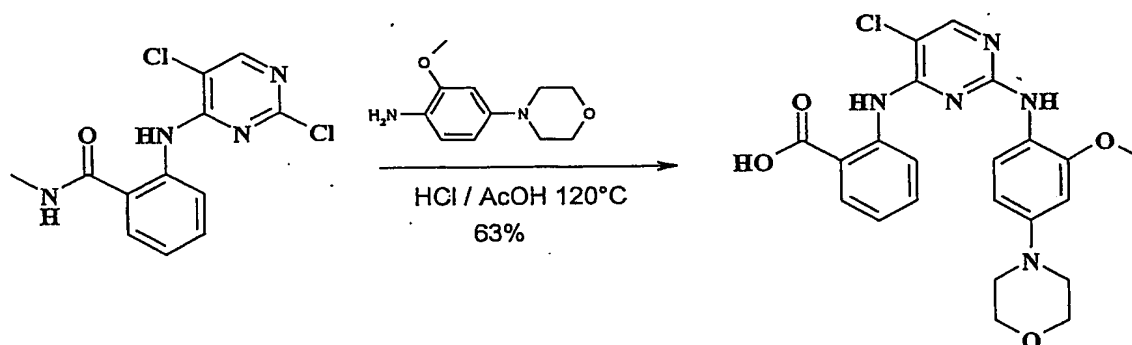
Preparation of 2-(2,5-dichloro-pyrimidin-4-ylamino)-*N*-methyl-benzamide



To a solution of 15.0 g (99.8 mmol) of 2-amino-*N*-methyl-benzamide in DMF (300 mL) are added 2,4,5-trichloropyrimidine (23.8 g, 130 mmol) and potassium carbonate (17.9 g, 130 mmol). The reaction mixture is stirred at 75°C for 5 hours, cooled to room temperature, and then poured into H₂O (600 mL). The resulting precipitate is collected by a filtration followed by washing with 50% aqueous CH₃CN (200 mL) and dried under reduced pressure (40°C, 10 hours) to give the desired 2-(2,5-dichloro-pyrimidin-4-yl-amino)-*N*-methyl-benzamide as ivory solid (26.4 g, 88.9 mmol, 89%).

NMR (400MHz, DMSO-d₆, δ): 2.81 (d, 3H, J = 4.52 Hz), 7.22 (dd, 1H, J = 8.56, 8.04 Hz), 7.60 (ddd, 1H, J = 8.56, 8.56, 1.0 Hz), 7.81 (dd, 1H, J = 8.04, 1.0 Hz), 8.48 (s, 1H), 8.52 (d, 1H, J = 8.56 Hz), 8.80-8.90 (m, 1H), 12.18 (s, 1H).

Preparation of 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-benzoic acid



To a solution of 1.0 g (3.37 mmol) of 2-(2,5-dichloro-pyrimidin-4-ylamino)-*N*-methyl-benzamide in 15 mL of acetic acid are added 2-methoxy-4-morpholinoaniline dihydrochloride (1.9 g, 6.73 mmol) and 6.0 mL of 1N ethanolic solution of hydrogen chloride (6.0 mmol). After the reaction mixture is stirred at 120°C for 16 hours and cooled to room temperature, aqueous NaHCO₃ solution is added to adjust the acidity between pH 5 and pH 6. The resulting precipitate is collected by a filtration and dried under reduced pressure to give 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenyl-amino)-pyrimidin-4-ylamino]-benzoic acid (970 mg, 2.12 mmol, 63%) as ivory solid.

NMR (400MHz, DMSO-d₆, δ): 3.10-3.20 (m, 4H), 3.78 (s, 3H), 3.70-3.80 (m, 4H), 6.52 (dd, 1H, J = 8.56, 2.52 Hz), 6.67 (d, 1H, J = 2.52 Hz), 7.08 (dd, 1H, J = 8.04, 8.04 Hz), 7.39 (d, 1H, J = 8.56 Hz), 7.35-7.45 (m, 1H), 7.99 (dd, 1H, J = 8.04, 1.52Hz), 8.14 (s, 1H), 8.28 (s, 1H) 8.70-8.80 (m, 1H).

Example 9: Sulfonamide moieties are prepared as follows:

Preparation of 2-amino-4-chloro-5-methyl-benzenesulfonyl chloride

To a solution of 2-amino-5-chloro-4-methyl-benzenesulfonic acid (3.0 g, 1.35 mmol) in dichloroethane (10 mL) is added sulfuryl chloride (4.4 mL, 3.83 mmol) and stirred at 60°C. After one hour, thionyl chloride (1.3 mL) is added and the mixture is further stirred at 100°C for 7.0 hours. The mixture is poured into iced water and extracted with ether three times. The organic layer is washed with water and then brine, dried over sodium sulfate, and evaporated in vacuo.

¹H-NMR (δ , ppm) : 2.35 (s, 3H), 6.68 (s, 1H), 7.75 (s, 1H).

This substituted sulfonyl chloride is reacted with a suitable amine. On reaction e.g. with methylamine, 2-amino-5-chloro-4,*N*-dimethylbenzenesulfonamide is formed.

Additional specifically preferred compounds according to the present invention that are useful either as FAK inhibitor, as ALK inhibitor or for inhibition of both and which may be prepared essentially according to the methods described hereinbefore are the following:

- 2-{2-[5-(1-Acetyl-piperidin-4-yloxy)-2-methoxy-phenylamino]-5-bromo-pyrimidin-4-ylamino}-N-methyl-benzenesulfonamide,
- N-[5-Bromo-2-(2,5-dimethoxy-phenylamino)-pyrimidin-4-yl]-N-(4-morpholin-4-yl-phenyl)-methanesulfonamide,
- 5-Bromo-N⁴-(4-fluoro-phenyl)-N²-(2-methoxy-4-morpholin-4-yl-phenyl)-pyrimidine-2,4-diamine,
- 2-[5-Chloro-2-(2-methoxy-4-piperazin-1-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide,
- 2-[5-Bromo-2-(5-fluoro-2-methoxy-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide,
- 2-[5-Chloro-2-(5-fluoro-2-methoxy-phenylamino)-pyrimidin-4-ylamino]-N-isobutyl-benzenesulfonamide,
- 2-{5-Chloro-2-[2-methoxy-5-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-pyrimidin-4-ylamino}-N-methyl-benzenesulfonamide, and
- 4-Cyclohexylmethoxy-6-[(1-ethyl-pyrrolidin-2-ylmethyl)-amino]-pyrimidine-2-carbonitrile.

Example 10: FAK Assay

All steps are performed in a 96-well black microtiter plate. Purified recombinant hexahistidine-tagged human FAK kinase domain is diluted with dilution buffer (50 mM HEPES, pH 7.5, 0.01% BSA, 0.05% Tween-20 in water) to a concentration of 94 ng/mL (2.5 nM). The reaction mixture is prepared by mixing 10 μ L 5x kinase buffer (250 mM HEPES, pH 7.5, 50 μ M Na₃VO₄, 5 mM DTT, 10 mM MgCl₂, 50 mM MnCl₂, 0.05% BSA, 0.25% Tween-20 in water), 20 μ L water, 5 μ L of 4 μ M biotinylated peptide substrate (Biot-Y397) in aqueous solution, 5 μ L of test compound in DMSO, and 5 μ L of recombinant enzyme solution and incubated for 30 min at room temperature. The enzyme reaction is started by addition of 5 μ L of 5 μ M ATP in water and the mixture is incubated for 3 hours at 37°C. The reaction is terminated by addition of 200 μ L of detection mixture (1 nM Eu-PT66, 2.5 μ g/mL SA-(SL)APC, 6.25 mM EDTA in dilution buffer), and the FRET signal from europium to allophycocyanin is measured by ARV0sx+L (Perkin Elmer) after 30 min of incubation at room temperature. The ratio of fluorescence intensity of 665 nm to 615 nm is used as a FRET signal for data analysis in order to cancel the colour

quenching effect by a test compound. The results are shown as percent inhibition of enzyme activity. DMSO and 0.5 M EDTA are used as a control of 0% and 100% inhibition, respectively. IC₅₀ values are determined by non-linear curve fit analysis using the OriginPro 6.1 program (OriginLab).

The Biot-Y397 peptide (Biotin-SETDDYAEIID ammonium salt) is designed to have the same amino acid sequence as the region from S392 to D402 of human (GenBank Accession Number L13616) and is prepared by standard methods.

Purified recombinant hexahistidine-tagged human FAK kinase domain is obtained in the following way: Full-length human FAK cDNA is isolated by PCR amplification from human placenta Marathon-ReadyTM cDNA (Clontech, No. 7411-1) with the 5' PCR primer (ATGGCAGCTGCTTACCTTGAC) and the 3' PCR primer (TCAGTGTGGTCTCGTCTGCCC) and subcloned into a pGEM-T vector (Promega, No. A3600). After digestion with *AccIII*, the purified DNA fragment is treated with Klenow fragment. The cDNA fragment is digested with *BamHI* and cloned into pFastBacHTb plasmid (Invitrogen Japan K.K., Tokyo) previously cut with *BamHI* and *StuI*. The resultant plasmid, hFAK KD (M384-G706)/pFastBacHTb, is sequenced to confirm its structure. The resulting DNA encodes a 364 amino acid protein containing a hexahistidine tag, a spacer region and a rTEV protease cleavage site at the N-terminal and the kinase domain of FAK (Met384-Gly706) from position 29 to 351.

Donor plasmid is transposed into the baculovirus genome, using MaxEfficacy DH10Bac *E.coli* cells. Bacmid DNA is prepared by a simple alkaline lysis protocol described in the Bac-to-Bac[®] Baculovirus Expression system (Invitrogen). Sf9 insect cells are transfected based on the protocol provided by the vendor (CellFECTIN[®], Invitrogen). The expression of FAK in each lysate is analysed by SDS-PAGE and Western blotting with anti-human FAK monoclonal antibody (clone #77 from Transduction Laboratories).

The virus clone that shows the highest expression is further amplified by infection to Sf9 cells. Expression in ExpressSF+[®] cells (Protein Sciences Corp., Meriden, Connecticut, USA) gives high level of protein with little degradation. Cell lysates are loaded onto a column of HiTrapTM Chelating Sepharose HP (Amersham Biosciences) charged with nickel sulfate and equilibrated with 50 mM HEPES pH 7.5, 0.5 M NaCl and 10 mM imidazole. Captured protein is eluted with increasing amounts of imidazole in HEPES buffer / NaCl, and further purified by dialysis in 50 mM HEPES pH 7.5, 10% glycerol and 1 mM DTT.

Example 11: Cell-free ZAP-70 Kinase assay

The ZAP-70 kinase assay is based on time-resolved fluorescence resonance energy transfer (FRET). 80 nM ZAP-70 are incubated with 80 nM Lck (lymphoid T-cell protein tyrosine kinase) and 4 μ M ATP in ZAP-70 kinase buffer (20 mM Tris, pH 7.5, 10 μ M Na_3VO_4 , 1 mM DTT, 1 mM MnCl_2 , 0.01 % BSA, 0.05 % Tween-20) for 1 hour at room temperature in a siliconized polypropylene tube. Then, the selective Lck inhibitor PP2 (1-tert-butyl-3-(4-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamine; Alexis Biochemicals) is added (final concentration 1.2 μ M) and incubated for further 10 min. 10 μ L of this solution is mixed with the 10 μ L biotinylated peptide LAT-11 (1 μ M) as substrate and 20 μ L of serial dilutions of inhibitors and incubated for 4 hours at room temperature. The kinase reaction is terminated with 10 μ L of a 10 mM EDTA solution in detection buffer (20 mM Tris, pH 7.5, 0.01 % BSA, 0.05 % Tween-20). 50 μ L europium-labelled anti-phosphotyrosine antibody (Eu-PT66; final concentration 0.125 nM); and 50 μ L streptavidin-allophycocyanine (SA-APC; final concentration 40 nM) in detection buffer are added. After 1 hour incubation at room temperature fluorescence is measured on the Victor2 Multilabel Counter (Wallac) at 665 nm. Background values (low control) are obtained in the absence of test samples and ATP and are subtracted from all values. Signals obtained in the absence of test samples are taken as 100% (high control). The inhibition obtained in the presence of test compounds is calculated as percent inhibition of the high control. The concentration of test compounds resulting in 50% inhibition (IC_{50}) is determined from the dose-response curves. In this assay, the agents of the invention have IC_{50} values in the range of 10 nM to 2 μ M, preferably from 10 nM to 100 nM.

Recombinant ZAP-70 kinase is obtained as follows: A nucleic acid encoding full-length human ZAP-70 (GenBank #L05148) is amplified from a Jurkat cDNA library by RT-PCR and cloned into the pBluescript KS vector (Stratagene, California, USA). The authenticity of the ZAP-70 cDNA insert is validated by complete sequence analysis. This donor plasmid is then used to construct a recombinant baculovirus transfer vector based on the plasmid pVL1392 (Pharmingen, California, USA) featuring in addition an N-terminal hexahistidine tag. Following co-transfection with AcNPV viral DNA, 10 independent viral isolates are derived via plaque-purification, amplified on small scale and subsequently analyzed for recombinant ZAP-70 expression by Western Blot using a commercially available anti-ZAP-70 antibody (Clone 2F3.1, Upstate Biotechnology, Lake Placid, NY, USA). Upon further amplification of one positive recombinant plaque, titrated virus stocks are prepared and used for infection of Sf9 cells grown in serum-free SF900 II medium (Life Technologies, Basel, Switzerland) under defined, optimized conditions.

ZAP-70 protein is isolated from the lysate of infected Sf9 cells by affinity chromatography on a Ni-NTAcolumn (Qiagen, Basel, Switzerland).

Recombinant His-tagged ZAP-70 is also available from PanVera LLC, Madison, Wisconsin, USA.

LAT-11 (linker for activation of T cell): The biotinylated peptide LAT-11 (Biotin-EEGAPDYENLQELN) used as a substrate in the ZAP-70 kinase assay is prepared in analogy to known methods of peptide synthesis. The N- α Fmoc group of Fmoc-Asn(Trt)-oxymethyl-4-phenoxy-methyl-co(polystyrene-1%-divinyl-benzene), content of Asn approx. 0.5 mmol/g, is cleaved using piperidine, 20% in DMF. Four equivalents per amino-group of Fmoc-amino acid protected in their side chains [Asp(OtBu), Glu(OtBu), Asn(Trt), Gln(Trt) and Tyr(tBu)] are coupled using DIPCDI and HOBt in DMF. After complete assembly of the peptide chain the terminal Fmoc-protecting group is removed with piperidine in DMF as before. L(+)-biotinyl-amino-hexanoic acid is then coupled to the terminal amino group using DIPCDI and HOBt in DMF using four equivalents of the reagents for four days at RT. The peptide is cleaved from the resin support and all side-chain protecting groups are simultaneously removed by using a reagent consisting of 5% dodecylmethylsulfide and 5% water in TFA for two hours at RT. Resin particles are filtered off, washed with TFA and the product is precipitated from the combined filtrates by the addition of 10 to 20 volumes of diethyl ether, washed with ether and dried. The product is purified by chromatography on a C-18 wide-pore silica column using a gradient of acetonitrile in 2% aqueous phosphoric acid. Fractions containing the pure compound are collected, filtered through an anion-exchange resin (Biorad, AG4-X4 acetate form) and lyophilized to give the title compound. MS: 1958.0 (M-H)⁻¹

Example 12: Phosphorylation levels of FAK

Phosphorylation levels of FAK at Tyr397 was quantified by the sandwich ELISA. Mouse mammary carcinoma 4T1 cells (1×10^5) were plated in wells of 96-well culture plates and incubated with or without various concentrations of inhibitors for 1 h in Dulbecco's modified eagle medium containing 0.5% BSA. The medium was removed and cells were lysed in 200 μ L 50 mM Tris-HCl, pH 7.4, containing 1% NP-40, 0.25% sodium deoxycholate, 150 mM NaCl, 1 mM EDTA, 1 mM PMSF, 1 mM Na₃VO₄, 1 mM NaF, 1 μ g/mL aprotinin, 1 μ g/mL leupeptin and 1 μ g/mL pepstatin. After centrifugation, the supernatants were subjected to a sandwich ELISA to quantify the phosphorylated FAK and total FAK. Cell lysates were applied to 96-well flat-bottom ELISA plates which had been pre-coated with 100 μ L/well of 4 μ g/mL mouse monoclonal anti-

FAK antibody (clone 77, Becton Dickinson Transduction Laboratories) in 50 mM Tris-HCl, pH 9.5, containing 150 mM NaCl for 18 h at 4°C and blocked with 300 µL of BlockAce (Dainippon Pharmaceuticals Co.) diluted at 1:4 with H₂O at room temperature for 2 h. After washing with TBSN (20 mM Tris-HCl, pH 8.3, containing 300 mM NaCl, 0.1% SDS and 0.05% NP-40), total FAK was detected with 100 µL of 1 µg/ml anti-FAK polyclonal antibody (#65-6140, Upstate Biology Inc.), and phosphorylated FAK was detected with 100 µL of 0.25 µg/µL anti-phosphorylated FAK (Y397) antibody (Affinity BioReagents, #OPA1-03071) in BlockAce diluted at 1:10 with H₂O. After 1 h incubation at room temperature, plates were washed with TBSN and 100 µL of biotinylated anti-rabbit IgG (#65-6140, Zymed Laboratories Inc.) diluted at 1:2000 with BlockAce diluted at 1:10 with H₂O was incubated at room temperature for 1 h. After washing with TBSN, ABTS solution substrate kit (#00-2011, Zymed Laboratories Inc.) was used for color development. Absorbance at 405 nm was measured after 20 min incubation at room temperature. The concentration of compound causing 50% reduction of phosphorylation level of FAK was determined.

Example 13: Anchorage-independent tumor cell growth assay

Mouse mammary carcinoma 4T1 cells (5×10^3) were plated in 96-well Ultra low Attachment plates (#3474, Corning Inc.) in 100 µL of Dulbecco's modified eagle medium containing 10% FBS. Cells were cultured for 2 h and inhibitors were added at various concentrations in a final concentration of 0.1% DMSO. After 48 h, cell growth was assayed with the cell counting kit-8 (Wako Pure Chemical), which uses a water soluble tetrazolium salt WST8. Twenty µL of the reagent was added into each well and cells were further cultured for 2 h. The optical density was measured at 450 nm. The concentration of compound causing 50 % inhibition of growth was determined.

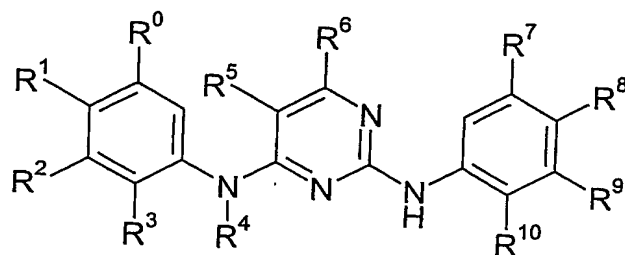
Table

The following test results were obtained using the methods described in Examples 9, 11 and 12:

Compound	FAK IC ₅₀ (nM)	phospho-FAK ELISA IC ₅₀ (nM)	4T1 cell growth IC ₅₀ (nM)
	Example 9	Example 11	Example 12
No. 1	140	0.7	>10
No. 3-1	44(37)	0.34	>10
No. 3-2	36	0.85	4
No. 3-3	9.1	0.14 (0.17)	0.5, 0.8 (2)
No. 3-4	32	0.53	2
No. 3-5	21(18)	0.07, 0.17 (0.1)	2, 1 (2)
No. 3-6	13	0.11	2
No. 3-7	16	0.45	2
No. 3-8	74	0.3	6
No. 3-9	48,24(16)	0.36, 0.5 (0.3)	0.7, 0.7 (2)
No. 3-10	52	0.95	>10
No. 3-11	9(8)	0.04, 0.02 (0.009)	0.3 (0.3)
No. 3-12	5.4	0.006	1
No. 3-13	58(49)	1.7, 0.5 (0.7)	0.6, 0.3 (3)
No. 3-14	54	0.4	5
No. 3-15	7	0.02, 0.02 (0.026)	0.8, 0.6 (1)
No. 3-16	48	1.1	3
No. 3-17	2.8	0.03, 0.02 (0.019)	0.1, 0.2 (0.3)
No. 3-18	130	1.5	9
No. 3-19	6.8	0.2, 0.35 (0.01)	0.3, 0.8 (0.2)
No. 3-20	16	0.22	0.3
No. 3-21	[22]	3	>10
No. 3-22	120	0.9	2
No. 3-23	38	0.39	0.5
No. 3-24	64	3.5	5
No. 3-25	22	0.3, 0.23 (0.25)	0.2, 0.3 (0.2)
No. 3-26	50	0.79	2
No. 3-28	43	0.71	0.7
No. 3-29	89	0.6	>10
No. 3-30	69	0.6	3
No. 3-31	13	1.1	5

Claims

1. A compound of formula I



(I)

wherein

each of R^0 , R^1 , R^2 , and R^3 independently is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkinyl, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkyl- C_1 - C_8 alkyl, C_5 - C_{10} aryl- C_1 - C_8 alkyl, hydroxy- C_1 - C_8 alkyl, C_1 - C_8 alkoxy- C_1 - C_8 alkyl, amino- C_1 - C_8 alkyl, halo- C_1 - C_8 alkyl, unsubstituted or substituted C_5 - C_{10} aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1, 2 or 3 hetero atoms selected from N, O and S, hydroxy, C_1 - C_8 alkoxy, hydroxy- C_1 - C_8 alkoxy, C_1 - C_8 alkoxy- C_1 - C_8 alkoxy, halo- C_1 - C_8 alkoxy, unsubstituted or substituted C_5 - C_{10} aryl- C_1 - C_8 alkoxy, unsubstituted or substituted heterocyclyloxy, or unsubstituted or substituted heterocyclyl- C_1 - C_8 alkoxy, unsubstituted or substituted amino, C_1 - C_8 alkylthio, C_1 - C_8 alkylsulfinyl, C_1 - C_8 alkylsulfonyl, C_5 - C_{10} arylsulfonyl, halogen, carboxy, C_1 - C_8 alkoxycarbonyl, unsubstituted or substituted carbamoyl, unsubstituted or substituted sulfamoyl, cyano or nitro; or

R^0 and R^1 , R^1 and R^2 , and/or R^2 and R^3 form, together with the carbon atoms to which they are attached, a 5 or 6 membered carbocyclic or heterocyclic ring comprising 0, 1, 2 or 3 heteroatoms selected from N, O and S;

R^4 is hydrogen or C_1 - C_8 alkyl;

each of R^5 and R^6 independently is hydrogen, C_1 - C_8 alkyl, C_1 - C_8 alkoxy- C_1 - C_8 alkyl, halo- C_1 - C_8 alkyl, C_1 - C_8 alkoxy, halogen, carboxy, C_1 - C_8 alkoxycarbonyl, unsubstituted or substituted carbamoyl, cyano, or nitro; and

each of R^7 , R^8 , R^9 , and R^{10} independently is C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkinyl, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkyl- C_1 - C_8 alkyl, C_5 - C_{10} aryl- C_1 - C_8 alkyl, hydroxy- C_1 - C_8 alkyl, C_1 - C_8 alkoxy- C_1 - C_8 alkyl, amino- C_1 - C_8 alkyl, halo- C_1 - C_8 alkyl, unsubstituted or substituted C_5 - C_{10} aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1, 2 or 3

hetero atoms selected from N, O and S, hydroxy, C_1 - C_8 alkoxy, hydroxy- C_1 - C_8 alkoxy, C_1 - C_8 alkoxy- C_1 - C_8 alkoxy, halo- C_1 - C_8 alkoxy, unsubstituted or substituted C_5 - C_{10} aryl- C_1 - C_8 alkoxy, unsubstituted or substituted heterocyclyloxy, or unsubstituted or substituted heterocyclyl- C_1 - C_8 alkoxy, unsubstituted or substituted amino, C_1 - C_8 alkylthio, C_1 - C_8 alkylsulfinyl, C_1 -

C₈alkylsulfonyl, C₅-C₁₀arylsulfonyl, halogen, carboxy, C₁-C₈alkoxycarbonyl, unsubstituted or substituted carbamoyl, unsubstituted or substituted sulfamoyl, cyano or nitro; wherein R⁷, R⁸ and R⁹ independently of each other can also be hydrogen; or R⁷ and R⁸, R⁸ and R⁹, and/or R⁹ and R¹⁰ form together with the carbon atoms to which they are attached, a 5 or 6 membered carbocyclic or heterocyclic ring comprising 0, 1, 2 or 3 heteroatoms selected from N, O and S; and salts thereof.

2. A compound of formula I according to claim 1, wherein

each of R⁰ or R² independently is hydrogen, C₁-C₈alkyl, hydroxyC₁-C₈alkyl, haloC₁-C₈alkyl, unsubstituted or substituted C₅-C₁₀aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C₁-C₈alkoxy, haloC₁-C₈alkoxy, C₅-C₁₀aryloxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC₁-C₈alkoxy, unsubstituted or substituted amino, C₁-C₈alkylsulfonyl, halogen, unsubstituted or substituted carbamoyl, unsubstituted or substituted sulfamoyl;

R¹ is hydrogen, C₁-C₈alkyl, hydroxyC₁-C₈alkyl, haloC₁-C₈alkyl, unsubstituted or substituted C₅-C₁₀aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C₁-C₈alkoxy, haloC₁-C₈alkoxy, C₅-C₁₀aryloxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC₁-C₈alkoxy, unsubstituted or substituted amino, C₁-C₈alkylsulfonyl, halogen, unsubstituted or substituted carbamoyl, unsubstituted or substituted sulfamoyl;

R³ is hydrogen, C₁-C₈alkyl, hydroxyC₁-C₈alkyl, haloC₁-C₈alkyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 heteroatoms selected from N, O and S, C₁-C₈alkoxy, substituted amino, C₁-C₈alkylsulfonyl, C₅-C₁₀arylsulfonyl, halogen, carboxy, substituted or unsubstituted carbamoyl, unsubstituted or substituted sulfamoyl; or

each pair of adjacent substituents R⁰ and R¹, or R¹ and R², or R² and R³ is -CH₂-NH-CO-, -CH₂-CH₂-NH-CO-, -CH₂-CO-NH-, -CH₂-CH₂-CO-NH-, -CH₂-NH-SO₂-, -CH₂-CH₂-NH-SO₂-, -CH₂-SO₂-NH-, -CH₂-CH₂-SO₂-NH-, -CH₂-CH₂-SO₂-, -CH₂-CH₂-CH₂-SO₂-, -O-CH₂-O-, or -O-CF₂-O-, and such pairs wherein hydrogen in NH is replaced by C₁-C₈alkyl;

R⁴ is hydrogen or C₁-C₈alkyl;

R⁵ is hydrogen; C₁-C₈alkyl, halogen, haloC₁-C₈alkyl, cyano or nitro;

R⁶ is hydrogen;

each of R^7 and R^9 independently is hydrogen, C_1 - C_8 alkyl, hydroxy C_1 - C_8 alkyl, halo C_1 - C_8 alkyl, unsubstituted or substituted C_5 - C_{10} aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1 - C_8 alkoxy, halo C_1 - C_8 alkoxy, C_5 - C_{10} aryloxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclyl C_1 - C_8 alkoxy, unsubstituted or substituted amino, C_1 - C_8 alkylsulfonyl, halogen, unsubstituted or substituted carbamoyl, unsubstituted or substituted sulfamoyl;

R^8 is hydrogen, C_1 - C_8 alkyl, hydroxy C_1 - C_8 alkyl, halo C_1 - C_8 alkyl, C_5 - C_{10} aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1 - C_8 alkoxy, halo C_1 - C_8 alkoxy, C_5 - C_{10} aryloxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclyl C_1 - C_8 alkoxy, unsubstituted or substituted amino, C_1 - C_8 alkylsulfonyl, halogen, unsubstituted or substituted carbamoyl, unsubstituted or substituted sulfamoyl, cyano, or nitro; and

R^{10} is C_1 - C_8 alkyl, hydroxy C_1 - C_8 alkyl, halo C_1 - C_8 alkyl, C_1 - C_8 alkoxy, unsubstituted or substituted heterocyclyl C_1 - C_8 alkoxy, unsubstituted or substituted amino, halogen, carboxy, carbamoyl, or unsubstituted or substituted sulfamoyl; or

each pair of adjacent substituents R^7 and R^8 , or R^8 and R^9 or R^9 and R^{10} , is $-NH-CH=CH-$, $-CH=CH-NH-$, $-NH-N=CH-$, $-CH=N-NH-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-O-$, $-CH=CH-O-$, $-O-CH_2-O-$, or $-O-CF_2-O-$.

3. A compound of formula I according to claim 1, wherein

each of R^0 or R^2 independently is hydrogen, C_1 - C_8 alkyl, halo C_1 - C_8 alkyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1 - C_8 alkoxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclyl C_1 - C_8 alkoxy, unsubstituted or substituted amino, or halogen;

R^1 is hydrogen, C_1 - C_8 alkyl, halo C_1 - C_8 alkyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1 - C_8 alkoxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclyl C_1 - C_8 alkoxy, unsubstituted or substituted amino, halogen;

R^3 is hydrogen, C_1 - C_8 alkyl, halo C_1 - C_8 alkyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 heteroatoms selected from N, O and S, C_1 - C_8 alkoxy, substituted amino, C_1 - C_8 alkylsulfonyl, C_5 - C_{10} arylsulfonyl, halogen, carboxy, substituted or unsubstituted carbamoyl, or unsubstituted or substituted sulfamoyl; or

each pair of adjacent substituents R^0 and R^1 , or R^1 and R^2 , or R^2 and R^3 is $-\text{CH}_2\text{-NH-CO-}$, $-\text{CH}_2\text{-NH-SO}_2\text{-}$, $-\text{CH}_2\text{-CH}_2\text{-SO}_2\text{-}$, $-\text{O-CH}_2\text{-O-}$, or $-\text{O-CF}_2\text{-O-}$, and such pairs wherein hydrogen in NH is replaced by $\text{C}_1\text{-C}_8\text{alkyl}$;

R^4 is hydrogen;

R^5 is hydrogen, halogen, $\text{haloC}_1\text{-C}_8\text{alkyl}$, or nitro;

R^6 is hydrogen;

each of R^7 and R^9 independently is hydrogen, $\text{C}_1\text{-C}_8\text{alkyl}$, $\text{haloC}_1\text{-C}_8\text{alkyl}$, unsubstituted or substituted $\text{C}_5\text{-C}_{10}\text{aryl}$, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, $\text{C}_1\text{-C}_8\text{alkoxy}$, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclyl $\text{C}_1\text{-C}_8\text{alkoxy}$, unsubstituted or substituted amino, halogen, unsubstituted or substituted carbamoyl, or unsubstituted or substituted sulfamoyl;

R^8 is hydrogen, $\text{C}_1\text{-C}_8\text{alkyl}$, $\text{haloC}_1\text{-C}_8\text{alkyl}$, $\text{C}_5\text{-C}_{10}\text{aryl}$, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, $\text{C}_1\text{-C}_8\text{alkoxy}$, $\text{haloC}_1\text{-C}_8\text{alkoxy}$, $\text{C}_5\text{-C}_{10}\text{aryloxy}$, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclyl $\text{C}_1\text{-C}_8\text{alkoxy}$, unsubstituted or substituted amino, halogen, unsubstituted or substituted sulfamoyl, or nitro; and

R^{10} is $\text{C}_1\text{-C}_8\text{alkyl}$, $\text{haloC}_1\text{-C}_8\text{alkyl}$, $\text{C}_1\text{-C}_8\text{alkoxy}$, unsubstituted or substituted heterocyclyl $\text{C}_1\text{-C}_8\text{alkoxy}$, unsubstituted or substituted amino, or halogen; or

each pair of adjacent substituents R^7 and R^8 , or R^8 and R^9 or R^9 and R^{10} , is $-\text{NH-CH=CH-}$, $-\text{CH=CH-NH-}$, $-\text{NH-N=CH-}$, $-\text{CH=N-NH-}$, $-\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-}$, $-\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-}$, $-\text{O-CH}_2\text{-O-}$, or $-\text{O-CF}_2\text{-O-}$.

4. A compound of formula I according to claim 1, wherein

each of R^0 or R^2 independently is hydrogen, piperazino, N-methylpiperazino or 1-methyl-4-piperidyloxy;

R^1 is hydrogen, piperazino, N-methylpiperazino, morpholino, 1-methyl-4-piperidinyloxy, 3-morpholinopropoxy or 2-morpholinoethoxy;

R^3 is sulfamoyl, methylsulfamoyl or propylsulfamoyl; or

the pair of adjacent substituents R^0 and R^1 , or R^1 and R^2 is $-\text{O-CH}_2\text{-O-}$, or the pair of adjacent substituents R^2 and R^3 is $-\text{CH}_2\text{-NH-CO-}$ or $-\text{CH}_2\text{-NH-SO}_2\text{-}$;

R^4 is hydrogen;

R^5 is hydrogen, chloro, bromo, trifluoromethyl or nitro;

R^6 is hydrogen;

each of R^7 and R^9 independently is hydrogen, C_1 - C_8 alkyl, halo C_1 - C_8 alkyl, unsubstituted or substituted C_5 - C_{10} aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1 - C_8 alkoxy, unsubstituted or substituted heterocycloxy, unsubstituted or substituted heterocyclyl C_1 - C_8 alkoxy, unsubstituted or substituted amino, halogen, unsubstituted or substituted carbamoyl, or unsubstituted or substituted sulfamoyl;

R^8 is hydrogen, C_1 - C_8 alkyl, halo C_1 - C_8 alkyl, C_5 - C_{10} aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1 - C_8 alkoxy, halo C_1 - C_8 alkoxy, C_5 - C_{10} aryloxy, unsubstituted or substituted heterocycloxy, unsubstituted or substituted heterocyclyl C_1 - C_8 alkoxy, unsubstituted or substituted amino, halogen, unsubstituted or substituted sulfamoyl, or nitro; and

R^{10} is C_1 - C_8 alkyl, halo C_1 - C_8 alkyl, C_1 - C_8 alkoxy, unsubstituted or substituted heterocyclyl C_1 - C_8 alkoxy, unsubstituted or substituted amino, or halogen; or each pair of adjacent substituents R^7 and R^8 , or R^8 and R^9 or R^9 and R^{10} , is $-NH-CH=CH-$, $-CH=CH-NH-$, $-NH-N=CH-$, $-CH=N-NH-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-O-CH_2-O-$, or $-O-CF_2-O-$.

5. A compound of formula I according to claim 1, wherein

each of R^0 or R^2 independently is hydrogen, piperazino, N-methylpiperazino or 1-methyl-4-piperidyloxy;

R^1 is hydrogen, piperazino, N-methylpiperazino, morpholino, 1-methyl-4-piperidinyloxy, 3-morpholinopropoxy or 2-morpholinoethoxy;

R^3 is sulfamoyl, methylsulfamoyl or propylsulfamoyl; or

the pair of adjacent substituents R^0 and R^1 , or R^1 and R^2 is $-O-CH_2-O-$, or the pair of adjacent substituents R^2 and R^3 is $-CH_2-NH-CO-$ or $-CH_2-NH-SO_2-$;

R^4 is hydrogen;

R^5 is hydrogen, chloro, bromo, trifluoromethyl or nitro;

R^6 is hydrogen;

each of R^7 and R^9 independently is hydrogen, methyl, isopropyl, trifluoromethyl, phenyl, o-, m- or p-methoxyphenyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, isopropoxy, phenoxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 2-(1-imidazolyl)ethoxy, dimethylamino, fluoro, morpholinocarbonyl, piperidinocarbonyl, piperazinocarbonyl or cyclohexylcarbamoyl;

R^8 is hydrogen, methyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, trifluoromethoxy, phenoxy, 1-methyl-4-piperidyloxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 3-(N-methylpiperazino)-propoxy, methylamino, fluoro, chloro, sulfamoyl or nitro; and

R^{10} is methyl, butyl, methoxy, ethoxy, 2-(1-imidazolyl)ethoxy, methylamino, dimethylamino or fluoro; or

the pair of adjacent substituents R^7 and R^8 or R^8 and R^9 is $-O-CH_2-O-$ or the pair of adjacent substituents R^9 and R^{10} is $-NH-CH=CH-$, $-CH=N-NH-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$ or $-O-CF_2-O-$.

6. A compound of formula I according to claim 1, wherein each of R^0 , R^1 or R^2 is hydrogen;

R^3 is sulfamoyl, methylsulfamoyl or propylsulfamoyl;

R^4 is hydrogen;

R^5 is chloro or bromo;

R^6 is hydrogen;

each of R^7 and R^9 independently is hydrogen, methyl, isopropyl, trifluoromethyl, phenyl, o-, m- or p-methoxyphenyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, isopropoxy, phenoxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 2-(1-imidazolyl)ethoxy, dimethylamino, fluoro, morpholinocarbonyl, piperidinocarbonyl, piperazinocarbonyl or cyclohexylcarbonyl;

R^8 is hydrogen, methyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, trifluoromethoxy, phenoxy, 1-methyl-4-piperidyloxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 3-(N-methylpiperazino)-propoxy, methylamino, fluoro, chloro, sulfamoyl or nitro; and

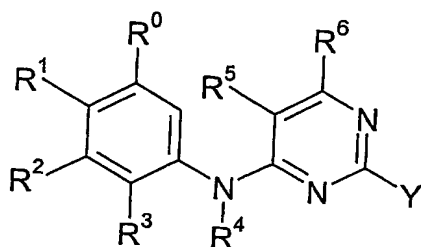
R^{10} is methyl, butyl, methoxy, ethoxy, 2-(1-imidazolyl)ethoxy, methylamino, dimethylamino or fluoro; or

the pair of adjacent substituents R^7 and R^8 or R^8 and R^9 is $-O-CH_2-O-$, or the pair of adjacent substituents R^9 and R^{10} is $-NH-CH=CH-$, $-CH=N-NH-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$ or $-O-CF_2-O-$.

7. The compound of formula I according to claim 1, wherein each of R^0 , R^1 or R^2 is hydrogen, R^3 is methylsulfamoyl, R^4 is hydrogen, R^5 is bromo, R^6 is hydrogen, each of R^7 and R^8 is methoxy, R^9 is hydrogen, and R^{10} is methyl.

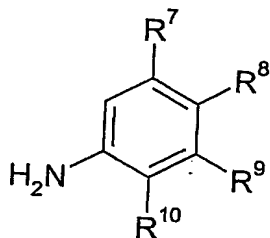
8. The compound of formula I according to claim 1, wherein each of R^0 , R^1 or R^2 is hydrogen, R^3 is methylsulfamoyl, R^4 is hydrogen, R^5 is bromo, R^6 is hydrogen, each of R^7 and R^8 is hydrogen, and the pair of adjacent substituents R^9 and R^{10} is $-\text{CH}_2\text{CH}_2\text{CH}_2-$.

9. A process for the production of a compound of formula I according to claim 1, comprising reacting a compound of formula II



(II)

wherein R^0 , R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are as defined in claim 1, and Y is a leaving group, with a compound of formula III



(III)

wherein R^7 , R^8 , R^9 and R^{10} are as defined in claim 1;

and, if desired, converting a compound of formula I, wherein the substituents have the meaning as defined in claim 1, into another compound of formula I as defined in claim 1;

and recovering the resulting compound of formula I in free form or as a salt, and, when required, converting the compound of formula I obtained in free form into the desired salt, or an obtained salt into the free form.

10. A pharmaceutical composition comprising a compound of formula I, wherein the substituents have the meaning as defined in claim 1, as active ingredient together with one or more pharmaceutically acceptable diluents or carriers.

11. The use of a compound of formula I, wherein the substituents have the meaning as defined in claim 1, for the manufacture of a medicament for the treatment or prevention of neoplastic diseases and immune system disorders.

12. A combination comprising a therapeutically effective amount a compound of formula I, wherein the substituents have the meaning as defined in claim 1, and one or more further drug substances, said further drug substance being useful in the treatment of neoplastic diseases or immune system disorders.

13. A method for the treatment of neoplastic diseases and immune system disorders in a subject in need thereof which comprises administering an effective amount of a compound of formula I, wherein the substituents have the meaning as defined in claim 1, or a pharmaceutical composition comprising same.

14. Use of a compound of formula I, wherein the substituents have the meaning as defined in claim 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of a disease which responds to inhibition of the anaplastic lymphoma kinase.

15. The use according to claim 14, wherein the disease to be treated is selected from anaplastic large-cell lymphoma, non-Hodgkin's lymphomas, inflammatory myofibroblastic tumors and neuroblastomas.

16. The use according to claim 14 or 15, wherein the compound of formula I is 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide or a pharmaceutically acceptable salt thereof.